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REPRODUCTION IN THE HUMAN FEMALE

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REPRODUCTION

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HUMAN FEMALE

THE UTERINE MUCOSA IN THE RESTING, MENSTRUAL AND PREGNANT STATES, AND THE FUNCTION OF THE DECIDUA

INCORPORATING AN ACCOUNT OF AN EARLY HUMAN OVUM

BY

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TO

DR. HAIG FERGUSON

FOR ENCOURAGEMENT AND GENEROUS HELP

PREFACE

This work is an account of the structure of the uterine mucous membrane and the functional changes which it undergoes during menstruation and pregnancy. An attempt has been made to throw light on many of the changes which have hitherto remained imperfectly understood, and to indicate the erroneous nature of much of the orthodox teaching on the subjects concerned. For the first time it is shown that the structural conformation of the uterine mucosa is intimately bound up with menstruation and with the processes associated with fœtal nutrition.

The investigations which are embodied in this work were carried out in the Royal Infirmary, and also, and largely, in the Laboratory of the Royal College of Physicians, Edinburgh. To the Superintendent, Dr. James Ritchie, I am indebted for the early human ovum described, and also for many kindnesses. To Dr. Haig Ferguson I am also indebted for much of the material. For the use of an early ovum, from which Plate XX. is taken, and for help, I am grateful to Dr. J. H. Teacher, of Glasgow.

Part of the work was incorporated in a thesis for the degree of M.D. in the University of Edinburgh.

The plates which illustrate the book are the work of Mr. Richard Muir, Pathological Department, University of Edinburgh, to whom I tender my warmest thanks for the great care taken in their production.

JAMES YOUNG.

Edinburgh, *August* 1911.

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CHAPTER I

STRUCTURE OF THE UTERINE MUCOUS MEMBRANE

The mucous membrane lining the uterine body in the resting state is seen to be of a greyish pink colour. It possesses a smooth or a gently undulating surface, which is seen, with the aid of a low magnifying glass, to be richly dotted over with small pits, the orifices of the glands. The thickness of the mucosa varies greatly under different circumstances, but in the adult resting uterus it is about 2 to 3 mm. Under the microscope the line of demarcation between mucosa and muscle is not even, but is thrown into irregular depressions and elevations, so that the two structures in this way interdigitate with one another. In some places the mucous membrane projects for a considerable distance into the muscular coat. The main mass of the mucous membrane consists of the interglandular connective tissue or stroma. In this numerous blood-vessels and glands are present; the latter open on the free surface, which is covered by a single layer of columnar cells.

The Surface Epithelium

The columnar cells forming this layer have a distinct ciliated margin. They are, for the most part, closely packed together, though here and there they may be separated by spaces in which small cells are present. The nuclei are usually oval in shape and are situated towards the base of the cells. Under some circumstances they become more rounded, and they rise up towards the centre of the cell body. Where the epithelium is lifted up in any condition—and this applies, also, to the cells forming the glands—it is often seen that the bases of the cells are connected with the stroma elements by means of protoplasmic filaments.

The Glands

These are of the tubular variety and are for the most part unbranched. In some places, especially towards their deeper parts,

they may divide into two, or, more rarely, three branches. They usually run somewhat obliquely to the surface, and in the ordinary resting stage of the mucosa they pursue a course which is fairly straight. In some conditions, *e.g.* menstruation, and in pathological states, they present a tortuous or corkscrew-like appearance. This is sometimes exhibited to a very marked degree.

The glandular epithelium resembles that covering the surface of the mucosa, consisting, namely, of columnar ciliated cells. The gland lumen is round on transverse section and oval on oblique section.

The glands can, for the most part, be traced in serial sections throughout the entire thickness of the mucosa, right to the muscular coat. Here they sometimes commence in slightly bulbous expansions. In some places they are seen to burrow into the muscle, sometimes, even under normal circumstances, for a considerable distance. They are seen to be imbedded in the portions of the stroma which project between the superficial muscle bundles.

With regard to the presence or absence of a specialised basement membrane immediately under the epithelial cells of the surface and of the glands, and comparable to similar structures found elsewhere, there is still a difference of opinion in the literature. This subject will be approached in a later part of this work; suffice it for the present to state that in some parts of the mucosa a layer of flattened cells may be seen under the bases of the columnar cells which apparently differ from the adjacent stroma cells.

The Interglandular Connective Tissue

This, as has already been stated, comprises the main mass of the mucous membrane of the uterus. The structural features of this tissue, with which we are especially concerned, has been described in widely different ways by different observers, and round it a large amount of literature has grown within recent years. The wide divergence of opinion, which becomes apparent even after a cursory glance through the literature, would seem to be dependent, to a large extent, on the many and varying appearances which the uterine mucosa exhibits. So great are the differences within normal limits that two perfectly healthy specimens from the same uterus may present histological characters so widely divergent as almost, at first sight, to justify the opinion that they have been derived from entirely different sources. This fact will be borne out in the course of this work.

Under the microscope the interglandular stroma of the mucosa is seen to consist, under ordinary circumstances, of nuclei densely packed together, each surrounded by a layer of protoplasm of varying thickness. The cells are seen to be separated from one another by clear intercellular spaces of varying size. Bridging across these spaces the adjacent cells are connected with one another by protoplasmic filaments. In most specimens, more marked in some than in others, a fine tissue network is seen between the cells. Coursing through the stroma arterioles are seen; they consist of the continuations of the ovarian and uterine arteries situated in the muscular coat, and pursue a spiral course throughout the stroma. They, for the most part, pass right to the surface, giving off small branches *en route;* here they break up into a fine capillary plexus, from which the blood is carried back to the muscular coat by means of veins with more poorly supported walls.

The difficulty of a correct structural interpretation of the apparently simple tissue just described has given rise to endless controversy. Henle[1]* stated that the stroma is formed by thickly-packed nuclei and cells, which sometimes grow into short rhombic plates. The spaces between the cells are filled with a finely granular material. On being teased out the cells are removed and a fine network is left behind. Frei maintained that it is composed of star- and spindle-shaped cells, which form a fine network; in this way it resembles the structure of a lymphatic organ. Krause considered it to be formed by spindle cells with long oval nuclei, and of rounded cells, which are connected with one another by processes in such a way as to produce a fine network. Kölliker believed it to be formed of spindle cells arranged singly or in bundles. In addition single round cells and a few free nuclei are present, all imbedded in an amorphous substance. Kundrat and Engelmann looked on the stroma as consisting of spindle and round cells lying in an amorphous intervening material. There is present, also, a fine network of threads, thicker in the deeper portions than at the surface. Robin considered the stroma as composed of embryonic ovoid, granular cells, separated by a finely granular amorphous material. In addition, spindle cells and connective tissue fibres are present.

One of the most important contributions to the literature was a paper published in 1874 by Leopold. As it will be necessary to refer frequently to the work of this observer, I shall consider his investigations in somewhat greater detail. According to him the interglandular

* The references to the literature are given at the end of the book.

stroma of the uterine mucosa consists of two distinct and separate entities, a connective tissue network, and a large number of flattened cells (*Zellplättchen* or *plättchenförmigen Zellen*). The connective tissue, which is continuous with the connective tissue between the bundles of the muscular wall, forms a scaffold or framework on which the stroma is built. When the surface of the muscle is reached the connective tissue bundles become separated into two different parts: the *outer* clothes the inner limit of the muscle and thereby separates it from the mucosa, whilst the *inner* passes between the glands and vessels as a fine network. These innermost connective tissue fibres become less and less evident as the surface is reached. The spaces of the network are lined throughout by the cell plates, and form a vast intercommunicating system filled with lymph. By experiment Leopold was enabled to inject this system from the subserous and intermuscular lymphatics, and he therefore concluded that the stroma is to be considered as an extensive lymphatic sponge, the cell plates corresponding to the endothelial cells of a lymphatic vessel. In animals (such as the pig, etc., in which his experiments were carried out) the spaces are larger and the cells are more widely separated than in the human uterus, to which, however, the same description applies.

The glands and blood-vessels run straight through this lymph-system, separated from the latter only by a layer of the connective tissue and the cell plates. These form the so-called basement membrane, and, massed round the endothelium and the blood-vessels in varying numbers, they produce the differing thickness of the vessel walls.

The arteries pursue a winding course from the muscle wall of the uterus to the surface, and there (often under the epithelium) they form a capillary network, from which the veins, situated mostly in the proximity of the arteries, carry the blood back to the muscle. Arterial twigs are often seen surrounding the glands. According to Leopold the finely granular material present in the intercellular spaces is coagulated lymph.

Championnière, in a work published in the year after that in which Leopold's investigations appeared, considers the mucosa, like this author, as forming a lymphatic surface.

According to Möricke (in a work which will be subsequently referred to in connection with the process of menstruation) the interglandular stroma is formed by round and spindle cells, some free nuclei, and an intervening finely granular amorphous material. The round

cells are distinctly granular. The other cells are oval or spindle-shaped, with a clear, glistening nucleus which fills almost the whole cell and only leaves a small amount of protoplasm at either pole. These cells are connected by means of long, fine filaments of protoplasm, which are often torn across. The free nuclei are oval; near them portions of protoplasm, resembling that found in the spindle cells, are seen. The nuclei, then, probably correspond to spindle cells which have lost their protoplasm. The connective tissue is arranged in the form of a fine network, in the meshes of which the round cells and a finely granular substance are present.

Poirier, like Leopold, looks on the uterine stroma as a lymphatic surface. Minot, in his *Human Embryology*, describes the uterine stroma as consisting of an undifferentiated embryonic tissue. Nagel believes that the stroma consists of a lymphatic tissue. Johnstone looks on it as an adenoid tissue. Williams agrees with Minot in considering the stroma as consisting of an embryonic tissue, and he moreover declares that " when preparations from the endometrium are treated by appropriate methods, an abundant reticulum can be demonstrated throughout its entire extent, which forms the scaffolding upon which it is constructed." He describes the arteries as pursuing a spiral course through the stroma, and breaking into a capillary network just beneath the surface epithelium. Webster also looks on the interglandular stroma as a tissue of low or embryonic type. " It is best described," he says, " as mainly consisting of delicate, anastomosing, nucleated masses of protoplasm."

This brief summary of the literature is sufficient to indicate the very varying and conflicting ideas entertained by different observers as to the structure of the stroma of the uterine mucosa. The main difference of opinion centres round the exact histological relationship between the cells of the stroma and the intervening branching and interlacing fibrils which form the network so frequently referred to. About the finely granular amorphous material or *Zwischensubstanz* there is less divergence of opinion; the larger number of observers agree with Leopold in considering it as coagulated lymph in the intercellular spaces. According to this same author the fibrillary network constitutes a separate and independent histological entity, and forms a sort of scaffold on which the stroma is constructed. The cells constitute an endothelium, which line the intercommunicating spaces of the connective tissue network, in this way forming a complex lymphatic surface or sponge. This belief is endorsed by many of the older writers; to-day it seems to commend

itself to only a few observers, though Williams would seem to believe in the existence of this network as a distinct and independent entity. Most of the workers in the subject lean towards the idea that the network is merely formed by the branching protoplasmic processes of the stroma cells. A fact which strikes one somewhat forcibly in the study of the literature on the subject is the meagre attention which has been given to the structure of the blood-vessels of the mucosa. This is all the more surprising in view of the fact that the structural changes which the stroma exhibits during menstruation and pregnancy are, at any rate in the initial stages, dependent on vascular alterations.

In conducting the following investigations I have employed almost entirely fresh specimens. This plan I have followed because of the readiness with which post-mortem change sets in. Like other recent observers I have used uteri removed entire, or specimens of the mucosa obtained by curettage. Specimens exhibiting a deviation from the well-established normal state of the glands, stroma, and vessels have been rejected. This has left, out of a much larger bulk of material, three complete uteri removed by operation and twenty scrapings. In many cases the examination has been carried out with the aid of serial sections. In this section many references are made to the specimens of the premenstrual and menstrual phases of the mucosa.

In the ordinary resting state the interglandular stroma is seen to consist of large numbers of cells. The nuclei are for the most part round or oval, and are frequently so densely packed together that only a comparatively small amount of cell protoplasm is visible. Under higher magnification the nuclei are seen to possess in most cases a close chromatic network. With special methods of staining some of the nuclei stain with the acid dye, others with the alkaline dye. The protoplasm of the cells is in some cases granular, in other cases sponge-like in nature. There is no evidence of a cell membrane; in fact in many cases it looks almost as if the meshes of the protoplasmic sponge communicate with the surrounding intercellular spaces. In many cases the outline of the cells is very irregular and ragged. Intervening between the cells there are distinct intercellular spaces; across these, however, the cell protoplasm is found to pass as strands, in this way establishing a direct protoplasmic communication between the contiguous cells (Fig. 1). These strands vary in thickness; in some cases they are stout, in other cases they are represented by the very finest filaments. It is often possible to recognise that these fibrils are composed of granules similar to those in the cell body, which are set

in a line, sometimes in single file. The intercellular spaces are usually clear; in other cases they are occupied by an amorphous material which takes on a faint eosin stain. In some cases portions of the stroma here and there may be seen to be represented by masses of protoplasm containing several nuclei—the differentiation into cellular units usually present becomes lost. This is an unusual condition, and is probably not to be considered as anything but rare in the normal resting stroma.

The communication between adjacent cells is brought out more clearly in œdematous conditions where the cells are spread apart; the protoplasmic filaments bridging across the enlarged intercellular spaces then become elongated, giving to the cells a distinctly stellate appearance (Plate I.). In many cases this protoplasmic communication is represented by a fine network uniting the contiguous cell surfaces. In some conditions this protoplasmic mesh-work may be present over a comparatively large area from which the nuclei and cells proper seem to have disappeared. This appearance may partly explain why some writers have been led to look on it as a tissue independent of, or at any rate not in direct structural continuity with, the cells. Leopold and others, as already mentioned, have considered the stroma as consisting of cell units entangled in its meshes. None of my specimens have suggested anything to lend favour to this conception; on the other hand, it is nearly always possible, with careful focussing, to determine that the fine filaments in the proximity of a cell amalgamate with its protoplasm, and that, in reality, the network consists merely of finely drawn out and branching portions of the cell substance. In support of this view, in addition to the above observation, may be mentioned the fact that it is often possible to determine that the amount of perinuclear protoplasm is inversely proportional to the number and length of the surrounding fibrils, suggesting that the body of the cell is drawn on to furnish the substance of the network. (Plates III. and IV.)

From these observations it will be obvious that the protoplasm of the stroma is a very variable structure. In some cases it is represented by a sort of multinucleated plasmodium; in other cases, and this is the normal state, the individual cells, though separated from one another by intercellular spaces, are found attached by bridging processes of a simple nature. In still other cases the protoplasm of the cells is drawn out to form branching processes united to produce a fine and intricate network.

The structural differences between the stroma cells are found to

involve the protoplasm of the cell bodies chiefly. The nuclei, however, are found to exhibit many and diverging differences in staining character, size, and shape. The variations in shape which the nuclei exhibit have led many observers to recognise and describe cells of different kinds. In some of the cells the nuclei are round, in others they are oval, in still others they become drawn out into rods. It seems more rational to explain these structural differences as representing changes in cells of the same order, due in the main to mechanical influences. A striking and convincing proof of this statement is as follows:—In the ordinary resting state the interglandular connective tissue, say in the superficial part of the mucosa, is composed of cells densely packed together. The nuclei are round or oval, and in the main the shape assumed by the surrounding protoplasm corresponds to the shape of the nucleus. Where the cells are most densely packed together one finds that the oval or rod-like nuclei predominate, whilst where the tissue is more open the nuclei and cells approximate more to the round shape. Immediately bordering on the gland the stroma cells are sometimes markedly flattened, and the nuclei are represented by fine rods which nestle close up to the epithelial cells; they then constitute the so-called basement membrane of the glands. At first sight these well-marked differences in contour would justify the conclusion that we are dealing with cells of different orders, such as are described by many writers. This conclusion, however, is strongly negatived by the fact that in the presence of certain normal functional changes in the mucosa these cell differences become obscured and often disappear entirely. If we still, for the sake of argument, limit our remarks to the more superficial portion of the mucosa (though, it should be noted, the same statements apply to the other regions), we find that during the premenstrual stage, in which the mucosa becomes greatly thickened, due to an opening out of the stroma spaces by an œdematous escape from the blood-vessels, the cells assume for the most part a round or stellate character (Plates I. and II. and Figs. 2 and 4). The point of importance is that the previously existent discrepancies in form have become greatly diminished, and in most parts completely lost. The only feasible and logical conclusion from this observation is that the cells of the stroma in reality consist of units identical in structure. A possible exception must be made to this general statement in view of the observation previously recorded, namely, that with special methods the nuclei of some of the cells take up the acid stain, while others absorb the alkaline stain. Of the signifi-

cance of this condition we are still unable to advance any conclusive statement; the attitude of histologists would seem to be in the direction of considering it an indication, not of the existence of cells of a different order and function, but of the presence of varying phases in the life-history of the same class of cell.

The stroma is seen from the above observations to approximate closely in structure to the developing mesoderm of the embryo, which consists of imperfectly differentiated cell units united with one another by branching protoplasmic filaments. The microscopic appearances presented by the stroma, and especially the homogeneous character it exhibits on certain occasions, justifies the conclusions of many observers, namely, that it consists merely of an undifferentiated embryonic connective tissue. Like the embryonic mesenchyme it is, perhaps, best considered as consisting of nucleated masses of protoplasm anastomosing with one another by means of finely-drawn-out parts of the perinuclear substance. Like the mesoderm of the embryo, also, the consistence of the protoplasm is probably more fluid than solid, in all likelihood approximating to that of a soft jelly. This point will be again referred to later on. It seems likely that the many variations in shape of the cell bodies and nuclei are to be accounted for by their ready response to any mechanical influence, and that when these are removed, as in the premenstrual phase, the cells are able, as it were, to draw themselves together and assume the contour of the characteristic round or stellate condition.

The condition described in relation to the stroma cells in general applies with equal force to the, at first sight, differentiated cells surrounding the glands—the so-called basement membrane—and those arranged round the vessels in concentric layers. Where the stroma elements are separated by œdema, or where the glands have shrunk away from the surrounding tissue, the elongated appearance of the nuclei and cell bodies is frequently completely dispelled, and the cells are then seen to be identical with the neighbouring stroma cells (Fig. 1). This observation suggests that the apparently specialised cells of the basement membrane have been moulded to their shape simply by being pressed up and flattened against the gland cells, and that, when this mechanical influence is removed, they are permitted to draw themselves together. No other interpretation, so far as I can see, can satisfactorily account for the appearances. Precisely the same description applies to the stroma cells surrounding the blood-vessels. The stroma round many of the vessels is represented by concentric

layers of elongated cells with oval or rod-like nuclei, this appearance becoming gradually replaced by the irregular disposition of the cells as the vessel is left (Fig. 3). Here, again, where the stroma cells are separated by a watery exudate, these appearances vanish completely, and the vessels are seen to be supported by cells differing in no respect from the ordinary stroma cell.

The following observations, whilst perhaps more appropriately studied in connection with the changes which the mucosa undergoes during menstruation, must be mentioned in this place in order to bring out one of the important characteristics of the stroma. That the consistence of the mucous membrane of the uterus is that of a soft, easily damaged structure is well known. It can be scraped with ease from the underlying firmer coat of muscle. The study of the microscopic character of the stroma furnishes us with important knowledge in this connection. Under ordinary circumstances, as already noted, the stroma consists of closely-packed cells, and the appearances then revealed by microscopic examination suggest at first sight that the stroma consists of a fairly compact and firm material. The study of the changes involved in the production of an œdematous or watery opening up of the tissue is found, on the other hand, to warrant the conclusion that the consistence of the stroma is, or at any rate can easily become, more that of a soft, almost fluid, medium. The nature of the displacement and spreading apart of the stroma elements in œdematous conditions is, perhaps, best studied in the immediate vicinity of the vessels. In these regions we frequently find the stroma cells becoming detached, apparently with ease, in concentric layers. The less supported outermost cells away from the vessel lumen become loosened more readily than the densely-packed cells which immediately abut on the vessel walls. After the displacement of the outermost cells there can occur a similar loosening and teasing out of the inner cells. This condition would seem to correspond to a uniform and universal fluid escape round the vessel circumference (Fig. 8). In still other cases the stroma cells appear to become ploughed up by the œdematous escape from one part of the vessel wall, and in this way a clear tract is created leading directly from the vessel lumen into the surrounding tissue. In this process the stroma cells are apparently readily displaced to either side by the escaping fluid. In still other cases the cells of the stroma in the neighbourhood of the vessel concerned are seen to radiate from the vessel wall, apparently wheeling into the line of the escaping fluid. It is often possible, in these cases, to recognise that the cells are

as it were, lifted off in concentric layers from the vessel wall. These observations demonstrate in a convincing manner the soft displaceable nature of the stroma protoplasm. The nuclei, which may be considered to correspond to more solid particles suspended in this semifluid medium, afford a ready index to positional changes in it.

In addition to the stroma cell, easily recognised by its branching protoplasmic filaments, round cells, with comparatively large nuclei and a smooth regular surface, are usually visible. These lie free in the stroma spaces, singly or in numbers, and in all probability correspond to leucocytes of the lymphocyte type. A careful study of my specimens has convinced me that, under normal conditions, the presence of those masses of leucocytes or *lymphoid nodules*, described by other observers, is only rarely detected. In addition to leucocytes, even in a normal resting mucosa, blood corpuscles are not infrequently encountered lying in the intercellular spaces of the stroma. These are of much more frequent occurrence towards the free surface of the mucosa, and where present are usually in the proximity of a blood-vessel. It seems likely that the intercellular spaces are occupied, as suggested by Leopold, by lymph, which in some cases becomes coagulated to form the finely granular amorphous substance often detected. Under abnormal circumstances one not infrequently discovers the deposit of filaments of fibrin in the spaces.

Structure of the Blood-Vessels of the Uterine Mucous Membrane

The uterine mucosa is provided with an exceptionally rich supply of blood-vessels. The arterial twigs reach the mucosa as the continuations of the smaller arteries found at the surface of the muscular coat. They pursue a tortuous course through the stroma, giving off small branches *en route*. In many cases the tortuous nature of the arteries is so intricate that such a sinuous vessel, when cut across in successive parts of its course in the same section, may give the impression of a bunch of arteries closely set together. For the most part the arteries appear to traverse the entire thickness of the mucosa, and do not break up into their capillary terminations till they reach the surface. Here these are not infrequently found to lie immediately subjacent to the surface epithelium. In many places, also, small branches are seen to lie in close proximity to, sometimes immediately in contact with, the epithelial cells of the glands. When the vessels are distended this

appearance is often brought out more clearly, and under these circumstances the vessels often seem to be more numerous in the neighbourhood of the glands than in the surrounding stroma. The blood is carried back by venous channels to the muscular wall of the uterus. The veins, for the most part, are found in the proximity of the arteries, and like these pursue a tortuous course.

In the resting state of the mucosa, as already mentioned, the vessels are convoluted, sometimes markedly so. It is interesting to note that in any condition which leads to an increase in the thickness of the mucosa, such as in the premenstrual stage, the vessels become drawn out, the flexuosities become opened out, and they are then seen to follow a course often perfectly straight for a considerable distance, a state which they never exhibit in the resting phase of the stroma (Plate I. and Fig. 13).

Structure of the Media of the Vessels of the Endometrium

In the resting state of the mucous membrane the vessels are lined by a layer of flattened cells, which are drawn out in the long axis of the vessel, corresponding to the direction of the blood flow. This is the usual condition, but not infrequently the blood is contained in channels whose immediate wall is formed by cells indistinguishable from the ordinary stroma cells; in these cases it looks as if the blood is contained in no proper blood-vessel, but is simply channelling the stroma (Fig. 5). The lining cells are supported, on their outer aspect, by cells which in most places are identical with the typical stroma cell. In some places, however, they are drawn out to encircle the vessels as concentric layers of a varying number. In this way the mucosal vessels exhibit apparently specialised walls, of differing thicknesses, resembling those of arterioles in other parts (Fig. 3). This concentric arrangement is often exaggerated in pathological conditions (Figs. 14 and 15).

When this appearance is present it is seen to become less and less marked as the region of the vessel wall is left, the concentric arrangement gradually fading away and becoming replaced by the more irregular disposition of the stroma cells. Whilst at first sight these cells look like cells more or less specialised for the performance of their supporting function, it seems probable that they consist, in reality, merely of stroma cells modified in no greater degree than can be easily explained by mechanical influences, in the same manner as the cells immediately bordering on the glands and surface epithelium are often flattened out by their being impressed on the flat surface of the bases

of the epithelial cells. In structure and staining characters the cytoplasm and nuclei of these cells differ in no respect from the surrounding cells of the stroma. They are connected with one another and with the surrounding cells of the stroma by means of protoplasmic filaments, a condition brought out with especial clearness after an œdematous teasing out of the stroma such as will be subsequently described in connection with the process of menstruation (Plate I.). A fact which brings home in a convincing manner the identity of the cells forming the vessel wall (and at the present moment we are still discussing all the cells external to the endothelium) and the ordinary stroma cells is that under these circumstances where there is an œdematous opening up of the stroma, all the differences previously existent, even those of shape and contour, become completely dispelled. During the premenstrual swelling of the mucosa it is interesting and convincing to note how the cellular distinctions become levelled, and this in every part of the stroma which exhibits the œdematous change. The ease with which this alteration in cell form is accomplished would appear to warrant one conclusion, and one conclusion only, namely, that the apparent differentiation of the cells indicates a change merely due to environmental circumstances, and that with the removal of these the cell differentiation disappears. It seems not unlikely that the lateral pressure exercised by the blood in the vessels is sufficient to explain the appearances; this will act in such a way as continually to tend to open out the vessel walls. With the soft, pliable nature of the stroma substance this pressure is readily transmitted to the surrounding cells.

This description of the vessel walls, with an occasional exception to be presently mentioned, applies to the vessels in every part of the mucosa, from the deepest incursions of the stroma into the superficial part of the muscularis to the free surface of the mucosa. It applies equally to the largest and best-supported vessels and to the smallest and most tender vessels at the surface. If possessed of a specialised wall at all, they must possess it only by virtue of the fine, single-celled internal lining. Our research, so far, drives us to the conclusion that the vessel walls are so constructed as to resemble those of capillaries in other regions of the body, or, at any rate, the fact that the support is formed only by the elements of the soft, mobile stroma which can easily become lifted off proves that they differ widely in structure from vessels of a similar thickness in other parts of the body. *The fact that structure elsewhere is always adapted to function would indicate that the remarkable appearances just noted are in all probability intimately bound up with the*

functional changes which the uterine mucosa undergoes during menstruation and pregnancy.

On Plate I. is represented an area of the uterine mucosa in the premenstrual stage. The stroma cells are separated by an œdematous exudate which brings out clearly the structural appearances which I have described. Throughout the section figured there has been, except in the immediate proximity of the vessels, a complete disappearance of the many and varied differences in cell form which are found in the resting and condensed state of the stroma. Instead of this the cells are found to have approximated to one type, the stellate cell. The adjacent cells are seen to be intimately connected with their neighbours by means of branching protoplasmic processes.

On the plate are represented two vessels, or rather two different levels of the same vessel. Both parts are distended, the upper more than the lower. The point which I wish more especially to indicate in this place is the fact that the opening out of the stroma has involved the region in the immediate vicinity of the vessels, and here it is obvious that we are dealing with the undifferentiated nucleated stroma protoplasm. In the portions of the stroma in this specimen, as also in others exhibiting the premenstrual condition where the teasing out of the cells by the œdema has occurred, there is invariably present the same change in the vessel walls. In no place can we detect the condensed arrangement of the stroma in concentric layers such as one sees in the resting mucosa.

As can readily be understood, the position just taken with regard to the structure of the vessels would be effectively weakened by the discovery of any muscular, fibrous, or elastic tissue as a structural component of their walls. There is a consensus of opinion in the literature that in no part of the mucosa, except occasionally in the vessel walls in the stroma immediately abutting on the muscularis, is there ever present muscular tissue. This my specimens fully confirm. It has been likewise clearly established by previous research that in the normal mucosa there is never found a formation of fibrous tissue. The nearest approximation to fibrous tissue is found in the spindle cells and their intercommunicating processes of soft protoplasm. The true nature of these elements I have fully discussed.

Elastic Tissue in the Endometrium

So far as I can discover there has been no exhaustive study in the literature in the direction of determining the exact quantity of elastic

tissue present in the mucosa of the uterus. In none of the papers to to which I have referred in the summary of the literature of the subject is it even mentioned. This, in view of the otherwise exhaustive nature of some of the investigations (Leopold, Möricke, etc.), is rather a remarkable omission. Most of the research in this connection has been concerned with the location and quantity of the elastic tissue in the muscular wall of the uterus, to which a notable contribution has been added within the last few months by Pankow. This author in a short paragraph touches on the site and amount of the elastic tissue in the mucosa. He states that whereas in a young girl, before the onset of menstruation, the vessels are devoid of an elastic coat, or, at most, possess fibrils visible only with the oil-immersion lens, during menstruation a distinct elastic layer appears. He has seen it in one case in a small vessel immediately under the surface of the mucosa. Weigert's stain was employed by Pankow to distinguish the elastic tissue.

For the purpose of testing the validity of these investigations I have examined all my specimens. To detect the presence of elastic tissue I have used Weigert's stain throughout. In all the sections of the normal mucosa (including 23 in the resting stage, 3 in the pre-menstrual stage of swelling, 7 during menstruation, and 2 immediately after) there was a complete absence of elastic tissue in the mucosa, except in the deepest incursions of the stroma into the superficial portion of the muscularis. In this region it is situated only here and there in the walls of the thicker vessels as a fine lamina just under the intima. It is completely absent in the surrounding stroma. Rarely the same appearances are detected in the deepest part of the stroma just external to the muscular coat. In no place were they encountered in the upper two-thirds of the mucosa.

Whilst the number of the specimens just cited would seem to justify a conclusion in direct opposition to that of Pankow, I have reinforced these observations by the same investigation in 40 other specimens of the uterine mucosa which I have been able to obtain through the kindness of Dr. James Ritchie of the Royal College of Physicians' Laboratory. These consist of scrapings obtained by the curette which were sent in for examination, and naturally comprise a large number of a pathological nature. Many of them, however (10 in number), were, so far as microscopic characters go, perfectly normal; the rest exhibited such abnormal conditions as œdema, hæmorrhage, and dilatation or hyperplasia of glands, none of which, I maintain, could have any influence in the direction of diminishing the elastic tissue present.

In these specimens the examination was identical in every respect with that above stated. The results in a tabular form work out thus:—

No Elastic Tissue found in the Upper Two-Thirds of the Uterine Mucosa in—

33	specimens	in the normal resting condition.
3	„	„ premenstrual stage.
9	„	during menstruation or immediately after.
11	„	with œdema and hæmorrhage.
19	„	with glandular dilatation or hyperplasia.
75	Total.	

On the strength of these observations I think we are justified in stating that the existence of elastic tissue either in the vessel walls or in the stroma of the upper regions of the uterine mucosa is, if ever present, of rare occurrence.

These investigations are in complete accord with the vascular changes which I have previously noted. In the beginning it seemed to me unlikely that vessel walls, which can open up in the remarkable manner described, could possibly be equipped with the support which an elastic-tissue layer would imply.

So far, then, we have seen that *for some reason or other the uterine vessels, almost immediately after reaching the mucosa, throw off their specialised supporting coats.* Here their walls external to the intima are formed entirely by the elements of the soft, mobile stroma, which in the thicker vessels is somewhat condensed to form a pseudo-media of varying thickness. Under certain circumstances, which have been indicated and the importance of which will be studied more in detail subsequently, the cells of this pseudo-media can become easily detached.

Structure of the Intima

The flattened cells which form the immediate lining of the walls of the mucosa vessels appear at first sight to be of the nature of a true endothelium, such as is found in other regions. That a specialised endothelial layer, however, is not an essential structural component of the stroma vessels is suggested by the fact which I have previously mentioned, namely, that in many regions the lining of the vessels is seen to be formed simply by unaltered stroma cells. In these cases the vessel wall often seems on examination to be constituted throughout

its entire thickness of cells, resembling in all respects the ordinary stroma cells (Fig. 5).

This observation, which one sees occasionally noted in the literature of the subject, suggested to me a line of inquiry in the direction of determining, if possible, whether the flattened cells found in most places forming the internal vessel lining are, in reality, to be considered as a specialised endothelium. These investigations, which have been carried out in a considerable number of uteri exhibiting all the phases in the functional variations to which the mucosa is subject, would tend to indicate that here again we are dealing not with cells which were in the course of their development bound to become specialised as an endothelial lining, but with cells which, in every respect, except perhaps in a way which is easily explained by the mechanical influence of the blood-stream, correspond to the stroma cells. As already mentioned, the protoplasm of the mucosa cells has retained its soft and pliable embryonic consistence. It is drawn out with ease into long, tender filaments, and it adopts with facility any shape impressed on it by any extracellular pressure. If packed together the stroma cells and nuclei are apt to assume an oval or rod-like contour; when, on the other hand, the tissues become opened out, the cells and nuclei tend to assume a more spherical shape, that, namely, characteristically chosen by cells free from unequal extraneous pressure, *e.g.* leucocytes.

The lining cells are seen, under the microscope, to be connected with the immediately adjacent cells by means of protoplasmic filaments, in this way establishing a resemblance to the typical stroma cell (Plates I. and II. and Figs. 2, 10, 11, and 12). The nuclei of these cells are found, in sections which cut the vessel longitudinally, to be drawn out in the long axis of the blood-vessel. In staining character and in structural appearances the resemblance between the lining cells and the surrounding stroma cells is perfect. In some cases, as already mentioned, the intimal cells are not even flattened out like an endothelial lining, and correspond in every respect, even as regards shape, to the stroma elements. The protoplasm of the lining cells is granular in appearance; in some cases, like the stroma cells, it may exhibit a sponge-like character, and here again the meshes of the sponge often seem, under the oil-immersion lens, to open out into the vessel lumen.

When the stroma cells become loosened and separated from the vessel wall by means of an œdematous exudate, the resemblance between the so-called endothelium and the adjacent cells becomes

even more manifest. With these they are seen to communicate by means of long protoplasmic strands or by means of a fine network. When the endothelial layer of the vessel is cut across tangentially it is often impossible to distinguish in any way its component cells from those of the adjacent stroma.

These appearances are well brought out in Plate I. At the regions in the vessels corresponding to the levels *a*, *f*, and *g* the endothelial layer is cut tangentially. The structural similarity of the cells to the adjacent stroma elements is convincingly demonstrated. At these regions the lining cells are often seen to be separated by spaces similar to the intercellular spaces of the stroma. Appearances similar to these are shown in Fig. 2. These observations at first sight strongly suggest that, in the opened-up stroma, the cells forming the vessel lining are separated by distinct intercellular spaces, and that, in this way, the vessel lumen communicates directly with the adjacent meshes of the stroma. As will be subsequently described, it would seem to be through these spaces that the blood corpuscles make their first escape into the surrounding stroma during menstruation. Through the interstices between the cells individual blood corpuscles are often seen escaping, and, on tracing a blood-track back to the vessel, the red cells are often seen streaming in quantity into the adjacent stroma.

As is well known, the uterine stroma is peculiarly liable to an œdematous or watery loosening and separation of its constituent cells. This condition is frequently detected in places in a mucosa in the resting stage which is perfectly normal in structure; as will be described in a subsequent section of this book, it occurs, also, as a normal process in the premenstrual and menstrual mucosa, and it would, in addition, seem to be a precursor of the decidual enlargement of the stroma cells in pregnancy. Its occurrence, also, is frequently noted in pathological conditions. Whilst these facts will be studied in greater detail in a later part of this investigation, they must be noted here in reference to their bearing on the question of the real structure of the lining cells of the vessel. During the premenstrual and menstrual alterations in the mucosa the vessels, especially those towards the surface, are found to dilate, sometimes to a considerable extent. In addition to this, however, they are often seen to open out by an entirely different process; the adjacent stroma cells become teased apart, the lining cells part company with one another, and, as it were, step back to range themselves alongside the displaced stroma cells (Figs. 2, 11, and 12 and Plate I.). *Under these circumstances it is impossible*

to tell which are the original intimal cells and which the stroma cells. The displacement of the cells in this process entails the severance of the intercommunicating protoplasmic fibrils binding them together. When this occurs it seems that the protoplasm is withdrawn within the cells, which then assume a more rounded contour. They lose completely their original flattened appearance and identify themselves in every respect with the surrounding cells of the stroma. These facts suggest strongly that the flattened, endothelium-like shape which they present is not only one impressed on the cells by mechanical influences, but is one from which they recover quickly when this influence is removed. They thus correspond closely with the so-called basement membrane of the glands. This is often constituted by a row of markedly flattened cells which abut on the gland cells. These are, as already demonstrated in all likelihood, not specially differentiated cells but merely cells of the stroma flattened against the gland; they lose their flattened appearance when released from the pressure. It is likely that the same considerations apply to the so-called endothelial cells of the stroma. These appearances are all shown on Plate I., which represents a condition of common note in the normal premenstrual mucosa. At the levels marked *d* and *g* the vessel walls are seen to be opening out. The flattened endothelial layer, possessing its ordinary characters at *c*, is seen at *d* to have opened out and to have been carried alongside the stroma cells to aid in the formation of the confines of the newly created blood space. Here it is impossible to tell which is original endothelium and which is stroma cell. The same appearances are detected at other parts of the vessel walls. In Fig. 19, also, are shown the changes associated with an opening out of the vessel walls. On one wall of the vessel, which has not shared in the process, the drawn-out, flattened cells of the intima are visible; on the other wall, in which the process is well marked, it is impossible to distinguish between the inner cells and the cells of the surrounding stroma.

I have previously demonstrated the fact that the walls of the vessel external to the endothelial layer are formed exclusively of stroma cells sometimes compressed together to lend greater support to the wall, but otherwise identical with the stroma cells. In this way we were led to the conclusion that the vessels of the stroma of the uterine mucosa must be considered to correspond in structure to capillary vessels in other regions. I have now advanced facts to prove that the so-called endothelial layer is, in reality, not composed of specialised cells but merely of stroma cells, in some cases unaltered even in form, whilst in

other cases they are flattened like a true endothelial lining. In the subsequent chapters of this work still further evidence will be adduced in support of the contention that the intimal and the stroma cell are structurally and functionally identical.

If, as these observations indicate, the so-called blood-vessels of the endometrium are in reality simply undifferentiated tracks through the stroma, we would expect to find that the larger vessels in the deeper part of the mucosa would conform in structure with the fine capillary twigs towards the surface. That this is the case is a fact of easy demonstration, and, as I have pointed out, it is interesting and instructive to note that the comparatively thick-walled arterioles in the muscle wall, with a distinct endothelial lining and a wall formed by muscle cells and elastic fibres, apparently throw off their supporting coats almost immediately the stroma is reached. In none of the specimens is there any evidence of muscle, fibrous or elastic tissue in any part of the uterine stroma except that adjacent to the muscular coat. Where the vessels require an extra support they derive it through a condensation of the neighbouring tissue cells.

In this place attention must be called to observations made by Leopold in connection with the structure of the stroma of the uterine mucosa. In his work he has clearly demonstrated in the human subject and in some of the lower animals the structural resemblances between the intima and supporting cells of the vessel wall and the cells of the stroma. The great importance of this observation would seem to have been somewhat obscured by the fact that more recent workers on the subject have demonstrated the fallacy of Leopold's statement that the cells of the stroma consist of round or oval plates, for the most part independent of one another. The connective tissue fibrils which often form a complicated network we now know do not, as Leopold maintained, constitute a completely independent structural entity, but are in reality merely drawn-out processes of cell protoplasm.

These erroneous observations led Leopold to the belief that the cells are in reality endothelial plates, which, set side by side, form a continuous endothelial lining for the lymphatic sponge of which the stroma consists. The cells forming the walls of the blood-vessels are also, according to Leopold, endothelial in nature; the thicker-walled vessels, as well as the finer, consist throughout of these endothelial plates. I mention those observations of Leopold as they, to a certain extent, confirm my own investigations, although my research has led to an entirely different interpretation of the appearances presented.

Do the Intercellular Spaces Communicate?

Throughout this record it has been mentioned that the appearances presented by the mucosa at first sight suggest that the intercellular spaces form an intricate network of fine tracks freely communicating with one another, and that, in this way, the mucosa, as Leopold first suggested, constitutes a sort of lymph sponge. This interpretation of the structure is derived from two separate observations. (1) The protoplasmic connections between the cells are usually represented in section as fine filaments, and these certainly appear under the microscope like threads stretching across the spaces, and the conditions suggest that, whilst just sufficient to connect the adjacent cells, they do not interrupt the communication between two neighbouring spaces. (2) In the second place Leopold was able to inject this intricate system of spaces from the lymphatic trunks in the muscular wall of the uterus and under the peritoneum. Are these two observations necessarily to be taken as proof positive of the usually accepted interpretation of the structure of the protoplasmic network of the stroma? My investigations have more and more convinced me that on this subject we may have been rather hasty in acceding to the teaching of Leopold and subsequent observers in view of the somewhat flimsy nature of the evidence advanced. It is obvious that an apparently thread-like connection between two adjacent cells would be the appearance revealed in section if this protoplasmic communication were of the nature of a complete film. In this respect, therefore, the evidence is not convincing. In the second place, the fact that colouring matter *injected under pressure* disseminated itself throughout the stroma does not necessarily prove the fact that the tissue spaces are in complete continuity. It is clear that a minimum pressure would suffice to rupture the fine protoplasmic films if such existed. The experiments no more convincingly and indisputably substantiate the orthodox conception than would the rupture of a soap-bubble with a pin-prick prove that the interior of the bubble was previously in direct communication with the outer air.

Whilst on such fine histological details it is impossible to dogmatise, I would submit the following observations in favour of the idea that the communications between the stroma cells are not of the nature usually supposed, *i.e.* threads of cell substance, but in reality consist of protoplasmic films, and that the intercellular spaces, in the resting state of the corresponding portion of the mucosa, are in this way completely shut in on every side.

1. I have shown how, in the opening out of the vessel walls, the endothelial cells are able to step back and range themselves alongside those of the stroma. (This I shall refer to in greater detail in the chapter on the Menstrual Changes.) Under these circumstances there is often an associated teasing apart of the stroma elements, with a marked widening of the intercellular spaces. According to the usually accepted idea, this opening up of the stroma should result in a freer communication than ever between the fluid tracks. The teasing out of the intimal cells is necessarily associated with a separation of the intervening connections. The result of these changes is that, in the end, the vessel wall is formed almost entirely of the stroma elements separated by the intercellular spaces, which, if the ordinary conception be correct, open directly into the vessel lumen, and by apertures much larger than the intercellular spaces of the resting stroma. Is this so? As we have shown, these changes result in a marked expansion of the vessel lumen, and this, in its turn, must be associated with a distinct increase in the lateral pressure of the blood fluid. This we would expect to determine at once a liberal and universal escape of the red cells into the adjoining tissue through the perforations in the wall, many of which are large enough to accommodate several red cells. The fact that this is not so, and that instead, whilst there has been a copious fluid escape, the red cells are for the most part retained in the lumen, and can often be seen to lie up against the vessel wall, strongly suggests, I submit, that this is not perforated, but complete. In several places, undoubtedly, the red corpuscles can be seen leaking through the wall, but this is sometimes only comparatively seldom, and only where a giving way of the tissue bridge between the lining cells can be seen to have taken place (Plate I.). If my interpretation, then, of the mode in which these blood spaces are formed be correct (and I shall substantiate it in the next chapter), we have strong evidence in favour of the fact that the protoplasmic connections passing between the cells are complete films and not mere threads.

2. Another observation of weight with regard to this question is to be found in the fact that the protoplasmic bridges between adjacent cells are almost invariably seen to be complete in the sections, *i.e.* one can almost always follow the wall of protoplasm completely round the intercellular space. This we can do both in the case of the smaller spaces and in the larger spaces. If these tissue bridges corresponded to filamentous processes we would almost certainly find that in sections they would be, in places, and probably in many places, completely

severed as the section cut them across. On the other hand, if they correspond to complete spherical films at various parts of whose surface the cells are situated, it is clear that, no matter the plane in which the section is made, the intercommunicating bridges will be invariably complete.

From these observations, then, it seems likely that the intercellular spaces, which form one of the chief structural characteristics of the mucosa, do not freely intercommunicate to form an intricate and complete network for a fluid circulation, but are, in reality, each a separate and distinct fluid space or "vacuole" separated from its neighbours by a protoplasmic film. As the existence and nature of these spaces seems to me to be of the greatest importance from the point of view of the structure of the stroma and the functions which this subserves, it will be necessary to study them in greater detail.

Structure of the Tissue Network of the Stroma

As has been shown by a study of the literature, the existence of this fine network in the uterine mucosa early attracted attention. By many observers it is looked upon as a structural entity completely independent of the stroma, whilst by others, and these the most recent workers on the subject, it is recognised as consisting of drawn-out portions of the protoplasm of which the stroma is formed.

One of the most remarkable features of the stroma which my investigations have revealed, is the striking variability in appearance which this structure exhibits. In the resting state of the stroma, when the cells are usually closely packed together, the protoplasmic bridges are, for the most part, simple and unbranched. In conditions associated with a teasing out of the stroma, on the other hand, it is usually found that this structure assumes an appearance of the greatest complexity. Instead of the straight, bridge-like process there is found between the adjacent cells an excessively intricate structure, on section looking like a finely-spun network. Instead of the simple intercellular space there are found a large number of spaces varying greatly in size, the smallest only recognisable with the oil-immersion lens, whilst others are visible with the low power of the microscope (Plates III. and IV.). These appearances will be discussed more fully in connection with the stroma changes in menstruation. In this place, however, an observation must be noted because of its importance in connection with the

probable nature of the intercellular space. With the appearance of this intricate protoplasmic structure it is often seen that there is a diminution in the amount and even a disappearance of the denser cell substance round the nuclei. In other words, it is clear that the cell cytoplasm has been drawn on to furnish the material of which the network is formed. The spaces are filled with a clear fluid, and, as I shall subsequently point out, it is likely that in this change we see the result of an active fluid imbibition by, and displacement of, the protoplasm of the stroma cells.

The structure of the stroma coincides closely in appearance with that of the mesodermic tissue of the developing embryo, and it has for this reason been considered by many observers as being nothing more than a primitive or embryonic connective tissue. This conception of the stroma my investigations amply confirm, but they have carried us still further in indicating that the lack of differentiation applies with equal force to the blood-vessels as to the surrounding stroma, and that, in fact, the vessels consist in their entirety of ordinary stroma cells which, if altered at all, are simply altered in a way easily explained by the influence of the blood-stream. The blood-vessels, in other words have no specialised wall, but consist merely of tracks or channels through the soft stroma protoplasm, by means of which a rich supply of blood is carried to every part of the mucous membrane.

During menstruation there is a liberal opening up of some of the vessels toward the surface; reasons will be adduced in a subsequent chapter to indicate that the structural peculiarities of the vessels of the stroma and of the stroma itself are such as to permit this to occur with the greatest possible efficiency. During pregnancy, also, there is an immediate and easy gaping of the vessels in the proximity of the embryo. The great perfection of this mechanism, also, would seem to be attributable in a large measure to the conformation of the vessel walls.

It would seem not unlikely that unusual function may demand unusual structure. The fact that the construction of the vessels of the uterine mucosa follows a different order from that of vessels elsewhere in the body would seem to be amply accounted for by the remarkable functions which they have to subserve. It has been shown in the preceding pages that the portions of the vessel walls corresponding to the media and externa in other regions of the body are formed, not by

musele or fibrous tissue, but merely by stroma whieh is eondensed in a measure proportional to the needs of the vessel, and in sueh a way as to offer no obstaele to a ready gaping of the vessel when oeeasion demands. This struetural peeuliarity at onee plaees the uterine vessels in a elass by themselves, and, this proved, the strueture elaimed for the intima is rendered not so unlikely as it otherwise might be.

Some reeent work on the eomparative histology of the blood-vessel system is of importanee in this eonneetion, and is suggestive in indicating that the eells entering into the eonstruetion of the vessel walls are not neeessarily sueh as were bound to subserve this funetion in the eourse of their development, and that the so-ealled endothelium may, at least under eertain eireumstanees, be derived direetly from the eonneetive tissue eells in the proximity of the vessel. It would tend, in other words, to indieate that the stroma of the uterine mueosa, whieh, after all, has for long been elassified as a rudimentary tissue retaining its embryonie eharaeter, has its prototypes in the animal kingdom. From Dahlgren and Kepner, in their *Principles of Animal Histology*, I would quote the following suggestive paragraph:—"The main blood-ehannel system itself has many differentiated regions—the region of thin-walled eapillaries and laeunæ, the strong-walled eonducting vessels and the blood-forming organs, and the museular pumping-stations or hearts. . . . Most speeifie of these portions are the eapillaries and laeunæ, for it is here that the region work of the blood is aeeomplished, the exehange of material with the tissues. Here the walls of the vessels are thinnest or even apparently wanting. In this ease the eonneetive tissue eells that surround the ehannel, while not differentiated into definite ehannel walls, aet in that eapaeity, so that we eannot say that retaining walls are altogether absent. . . .

"The internal tissue of a Turbellarian worm is a loose aggregate of several kinds of weakly differentiated eells, known as parenehyme. These eells do not toueh eaeh other at all points, but are conneeted by strands, and in eonsequenee there may be easily seen between them a great many spaees, known as the intereellular spaees, whieh are united into a large eonneeting system that extends throughout the body. This system of spaees is filled with a fluid, and this fluid earries the digested food materials—the oxygen supply for internal eells, the combustion produets—and in every other way aets as a simple blood-vessel."

In this deseription of a simple blood system we eannot fail to see an analogy to the strueture of the uterine mueosa as figured in the previous pages.

Summary

(1) The stroma of the uterine mucosa consists of a soft, semi-fluid, protoplasmic mass imperfectly differentiated into cellular elements.

(2) The cells are separated by intercellular spaces, which together form a complicated system occupied with clear fluid (ordinary lymph, according to Leopold).

(3) The cells anastomose freely with one another by means of protoplasmic processes. They present many and varying alterations in shape, but these are easily dispelled, and the cells then approximate to the typical round or stellate shape. The differentiation of the stroma cells is, thus, probably more apparent than real.

(4) The intercellular spaces, in all probability, do not communicate directly with one another. The anastomosing processes of the cells are probably not filaments, but films of protoplasm, which under ordinary circumstances close in the fluid cavities.

(5) The intima and media of the vessels, and the basement membrane of the glands, are nothing more than ordinary flattened stroma cells. This shape they easily lose.

(6) Except in the deepest layers of the mucosa, the vessels have no specialised supporting coats (muscle, elastic tissue).

(7) The vessels are obviously so constructed as to allow a ready and universal opening up of their walls, and the structure and consistence of the stroma such as to permit its ready displacement by fluid or blood. It would seem that these structural peculiarities must have some intimate bearing on the functional changes of menstruation and pregnancy.

CHAPTER II

MENSTRUATION

Many qucstions in regard to menstruation still await elueidation. This is particularly true in conneetion with the exact nature of the minute mieroscopical changes whieh the uterine mucosa undergoes, and in connection with the part whieh the ovary plays in thc proeess. In this plaee we are more eoncerned with the relationship whieh exists between the peculiar struetural conformation of thc endometrium, to which attention was drawn in the preceding ehapter, and the mueosa ehanges in menstruation. Before discussing this it will be necessary to review in brief the position which this subject occupies at the present day.

The General Anatomy of the Menstrual Cycle

The endometrium during the menstrual cyele undergoes a series of ehanges which are divided into the following stages:—

1. The Stage of Premenstrual Swelling.
2. The Stage of Bleeding.
3. The Stage of Repair.
4. The Stage of Quieseenec.

In the average female this cycle takes 28 days for its eompletion, 5 being dcvoted to the first stage, 4 to thc seeond, and 7 to the third. The fourth stage corresponds to thc endometrium in the resting stage, a full description of whieh has been given in the preeeding chapter. It corresponds to the interval of 12 days between the stages of regeneration and swelling.

1. *The Stage of Premenstrual Swelling.*—The mucosa beeomes swollen, due, it would seem, ehiefly to a serous infiltration of the tissues. The change involves the outer portions of the mucosa chiefly, and leads to a spreading of the glands apart. Thc cells become widely separated from one another with an elongation of the intercommunieating protoplasmic processes. Aeeording to Leopold, in this stage the mucosa increases in thickness from 2 to 3 mm. (eorresponding to the resting stage) to 6 to 7 mm., and thc walls of the uterine cavity beeome pressed

together. There is, in addition, a marked folding of the mucosa surface. Whilst the swelling is due chiefly to the œdematous opening out of the tissues, it is dependent partly on a distension of the vessels and on hæmorrhagic extravasations, and partly on a multiplication of the stroma cells. The blood escape into the stroma involves only the superficial regions, and is apt to lead to a lifting up of the surface epithelium in the form of small blisters (the subepithelial hæmatomata of Gebhard).

The glands become straightened and elongated. The first change is mechanical, the second dependent on an actual hypertrophy (Leopold). The gland lumina become increased. According to Westphalen, Lipes, and others this is due to an increased secretion, which is often seen lying in the lumen. The nuclei of the cells of the surface and gland epithelium are apt to become swollen, and to rise up towards the centre of the cell bodies.

One of the most characteristic changes in the mucosa during this and the ensuing stages consists in a marked softening. This has been pointed out by several observers, and was very evident in some of my specimens. According to Kundrat and Engelmann the softening occurs to such a degree as to make the mucosa almost fluid in consistence. According to Möricke it becomes soft and pulp-like. The importance of this fact I shall refer to subsequently.

2. *The Stage of Bleeding.*—The changes which the mucosa undergoes during this stage have given rise to long-continued controversy, and the question cannot be considered to be settled. Such investigators as Kölliker, Kundrat, and Engelmann, Sir John Williams, Wyder, v. Kahlden, Strassmann, and others described a complete or extensive detachment of the epithelium and stroma. Others, such as Underhill and Löhlein, believe that the separation and removal is limited in degree. Still others, Leopold, Möricke, de Sinéty, Jacobs, Gebhard, Findley, Whitridge Williams, etc., assert that there is little or no loss of tissue. Where it does occur it is probably accidental. The specimens which I have examined support the views held by these latter authors (Fig. 6). It is noteworthy that the workers who studied specimens obtained from the dead body were almost unanimous in describing the existence of a loss of tissue. This fact was first indicated by Leopold and Möricke, and it is now recognised that, for satisfactory study, only specimens obtained by operation, *i.e.* hysterectomy or curettage, should be employed.

The nature of the bleeding has given rise to considerable discussion. Some authors believe that it is dependent on a rupture of the vessel

walls, whilst others declare that it is ehiefly by a process of diapedesis. The commonly aceepted belief at the present time is that both proeesses are in operation. Those who hold that there is little or no loss of tissue believe that the red cells escape into the uterine cavity chiefly by passing between the epithelial cells of the surfaee and glands. At the plaees where the epithelial cells are lifted up and detached a larger blood escape occurs.

The extent of the area in the mueosa involved by the blood eseape has been differently described by various authors. Where this question is espeeially referred to, most authors would seem to agree with Mörieke, who says that the deeper and middle thirds of the mueosa remain immune to the ehange.

The changes in the mueosa responsible for the menstrual phenomena have attracted considerable attention. The oldest explanation is that advaneed by Kundrat and Engelmann and Sir John Williams, who attributed the bleeding to a fatty degeneration of the vessel walls and stroma, resulting in a mechanieal eseape of the vessel eontents. Leopold, Möricke, Wyder, and others, however, have proved that this fatty change, exeept in abnormal cireumstanees, is either absent altogether or is present only in a minor degree, and they have denied that it can in any way be considered as the causal agent.

The other explanation put forward to aeeount for the bleeding may be called the congestive theory. It was first enuneiated by Pflüger, and in different forms has been held by most workers up to the present time. The changes in the vessels and in the stroma during the premenstrual and the menstrual phases I shall discuss at greater length on subsequent pages.

3. *The Stage of Repair.*—This consists of the stage immediately succeeding the eessation of the blood flow. The deseriptions given of the mucosa at this time naturally vary as widely as the accounts of the tissue ehanges assoeiated with the menstrual flow. Some authors even state that at this time there is a detachment of the upper layers of the mueosa, which have lost their vitality as the result of the hæmorrhage. This may be associated with a fatty change (Martin, etc.).

Those workers who believe that the epithelium is only elevated in the last stage state that it sinks to its former level; where it is shed it is regenerated from the adjacent surfaee or gland epithelium; where the stroma is lost it is replaeed by a multiplieation of the remaining stroma elements, in which Westphalen noted an extensive mitotie division. The blood remaining in the tissues is absorbed for the most part; some,

however, may persist for a longer time, becoming transformed into a brownish pigment (Gebhard). The blood-vessels shrink to their former size. Where there has been a loss in the integrity of the vessel walls a new formation is necessary. Whether this is of the nature of a proliferation, or merely, as Heape has described in *Semnopithecus entellus*, of a rearrangement of the original cellular elements, has not been definitely proved.

Within recent years a large amount of investigation has been conducted into the cyclical changes which the uterine mucosa undergoes in the lower animals. This has resulted in an establishment of the essential similarity between those changes and those which occur in the human female.

The work of Heape on the menstrual cycle of *Semnopithecus entellus* and *Macacus rhesus*, and of van Herwerden on the cyclical uterine changes in *Cercocebus cynomolgus*, are of especial interest.

In Heape's investigations the changes were found to fall under four heads:—(*a*) The Period of Rest; (*b*) The Period of Growth; (*c*) The Period of Degeneration; (*d*) The Period of Recuperation. The first stage corresponds to the ordinary quiescent interval of the mucosa. The *growth of the mucosa* in the second stage is due to an extensive amitotic multiplication of the stroma elements of the superficial parts, and to an increase in size of the deeper vessels. The epithelia of the glands and surface remain unaltered in the earlier stage; later the glands become widened. There is also at a later stage a new formation of vessels towards the surface. In the *Stage of Degeneration* there is a widespread degeneration of all the elements of the superficial regions. There is breaking down of the walls of the vessels, due to an amyloid or hyaline change. The blood is poured into lacunæ, which burst through the degenerated epithelium and evacuate their contents into the uterine cavity. The disintegrated epithelium of the surface and glands and the upper layers of stroma, with blood and vessels, are detached as the "menstrual clot." In the *Stage of Recuperation* the detached epithelium is reformed from the glandular epithelium which remains, but also from the underlying stroma. The blood corpuscles remaining in the tissues are taken up by the developing vessels. "The protoplasm of the cells bounding these spaces (with the corpuscles) flattens out, the nuclei of the cells becoming also flattened and elongated, and numerous fine capillary vessels are thus formed, continuous with the deeper parts of the mucosa with large preexisting capillaries, and so with the circulatory system." The stroma elements multiply and the shed material is restored.

It will be noted that whilst in many points the cycle, as thus described in these monkeys, corresponds to that in the human female, in other points, *e.g.* the amount of tissue destruction, it differs widely from the orthodox conception regarding menstruation in man. The observations of van Herwerden in *Cercocebus cynomolgus* correspond closely to those of Heape.

The histology of the endometrium during the menstrual cycle has been studied by Marshall and Jolly in the case of the dog, and by Marshall in the ferret. Here the stages coincide closely with those found in the human and in the monkeys mentioned. In the dog and ferret the following phases were noted:—(1) The Period of Rest; (2) The Period of Growth and Congestion; (3) The Period of Destruction; and (4) The Period of Recuperation.

The researches of Heape and of Marshall and Jolly have revealed a fact of the greatest importance in connection with the relationship which exists between the œstrus cycle of the lower animals and the menstrual cycle in man. Menstruation can, in the light of their work, no longer be identified with the period of desire or œstrus in the lower animals. It corresponds to the period preceding this—the pro-œstrum. "Those who have denied that there is any correspondence between 'heat' and menstruation have laid stress upon the assertion that whereas 'heat' in the lower animals is the time for coition, this act, as a general rule, is not performed during menstruation. But, as was first pointed out by Heape, it is the pro-œstrum alone and not the entire 'heat period' (a term used generally to include both pro-œstrum and œstrus) which is the physiological homologue of menstruation; and, moreover, the latter process in many of the primates is succeeded by a regular post-menstrual œstrus. The physiological identity of the pro-œstrum with menstruation should always be kept in view in considering the cause and nature of the phenomena, since, as will be seen later, many strange errors have been committed, and wrong conclusions arrived at, through failure to realise the unity of the two processes" (Marshall *).

Whilst in the lower animals, as a general rule, the period during which the female will receive the male, and during which alone conception can occur, corresponds to the œstrus, in the human subject, as also in some animals, this arrangement has been modified. It would seem that in man coition may be successful at any stage of the menstrual cycle except the stage of bleeding (Bryce and Teacher †).

* *Physiology of Reproduction*, 1910, p. 110.

† *Early Development and Imbedding of Human Ovum*, 1908, p. 64.

CHANGES IN THE BLOOD-VESSELS AND THE STROMA DURING MENSTRUATION

It was pointed out in the preceding chapter that the stroma must be considered to be composed of a soft, multinucleated, protoplasmic mass occupied by a complex system of fluid spaces which break it up into poorly differentiated cellular elements. The spaces lie up against the perinuclear portions of the protoplasm and separate the cells from one another, except for bridging processes of the general protoplasmic mass (Plates I. and II.). This description applies to every part of the mucosa. I have adduced evidence which tends to indicate that the fluid spaces in the ordinary resting state do not communicate freely with one another, as is usually stated. It seems more likely that the bridges of protoplasm correspond to continuous films separating the adjacent fluid collections, which are thus contained in completely walled-in cavities or vacuoles. This conception will be further endorsed, and its importance will be revealed, in subsequent paragraphs. I have pointed out that the different cell forms detected in the stroma are not to be considered as indicating units differing in structure and function. The fact that these variations are easily dispelled during certain normal functional changes indicates that they are merely temporary in nature, and are, in all probability, dependent on environmental conditions, especially extracellular pressure. This was seen to apply also to the basement membrane of the glands.

I have pointed out that the blood-vessels merely consist of tracks through this uniform stroma. It is probable that the vessels throughout the extent of the mucosa derive their supporting coats exclusively from the surrounding stroma elements, which are unaltered in the performance of their function except that where the blood-pressure within the vessels is greater they become more condensed round the lumen, and in so doing often become drawn out tangentially to the vessel and arrange themselves in concentric layers. In the case of the arterioles the thicker the vessels (*i.e.* the nearer they are to the heart) the larger the number and the greater the condensation of the surrounding stroma cells, whilst in the case of the capillary twigs the wall is represented merely by a single layer of flattened-out stroma cells. The walls of the veins are constructed in a similar manner, but are thinner than their corresponding arteries. These facts apply with equal force to the media and intima. This interpretation of the structure of the mucosa vessels is borne out to a considerable degree by the fact that into the composition of their

walls there do not enter the differentiated structures found in vessels of a similar size in other regions of the body. In none of them, even the thickest, except in the very deepest portions of the stroma, is there ever present any muscular, fibrous, or elastic tissue. I have referred to the striking fact that, whereas the vessels in the muscular coat contain the ordinary muscular and elastic ingredients, these are lost almost immediately the stroma is reached. For some reason or other the vessels throw off their supporting coats in the mucosa, and I advanced the belief that such a structural arrangement must have its bearing on the changes in the vessels which occur in menstruation and pregnancy.

In the premenstrual phase there is a marked swelling of the mucosa, due, in the main, to distension of the blood-vessels, increased lymph escape, and blood extravasation. The latter is usually not marked except in the immediate proximity of the vessels. There is at the same time a *marked softening of the mucous membrane ; so manifest is this that the consistence becomes almost that of a jelly.* This fact has been specially noted by several observers—Kündrat and Engelmann say that "the softening occurs to such a degree as to make the mucosa almost fluid in consistence." Leopold refers to the same condition, Möricke states that the mucosa becomes "soft and pulp-like," and other observers bear testimony to the same effect. The slightest pressure is sufficient to injure the mucosa, and it can be scraped with the greatest ease from the underlying muscle coat. It seems to me that this may explain to a large extent the wide discrepancy evident in the literature regarding the amount of damage present in the menstrual mucosa. In fact, in scrapings removed from the uterus during this period it is not uncommon to find the blood and stroma mixed up intimately with one another in an artificial way, indicating that the consistence of the two materials has been somewhat of the same order. It can readily be understood how even gentle handling of a uterus in the operating theatre or the post-mortem room might be sufficient to damage the mucosa, and thus lead to erroneous conclusions. These facts, combined with the well-known readiness with which disintegration ensues after death, afford ample explanation of the conflicting results obtained by different observers.

The œdematous opening out of the stroma during menstruation involves chiefly the upper strata, and is absent, or only present to a small degree, in the part immediately adjacent to the muscle. The intercellular spaces become distended by the increased fluid escape; the protoplasmic bridges connecting the cells become drawn out and

attenuated—in many cases they become completely detached—and spaces of small or large size are produced in the stroma by a displacement of the cells. With the œdematous opening out of the tissue there occurs a marked alteration in the shape of the cells. They become rounded or stellate. In the œdematous stroma this is the only cell form present (Plate I.), with the exception of the leucocytes lying free in the spaces. We thus see that the changes associated with the menstrual function have led to the stroma cells becoming approximated to one type. The cellular distinctions become levelled; the oval and rod-like cells have disappeared, and they have identified themselves with the general mass of poorly differentiated protoplasm. It was observations of this nature which led to the interpretation of the stroma which I have previously formulated.

Mode of the Blood Escape

In the literature there is a considerable divergence of opinion regarding the exact manner in which the blood escapes from the vessels into the surrounding tissues during menstruation. Some observers consider that it occurs by a process of rupture, with a subsequent discharge of the contained blood into the surrounding tissues, whilst others maintain that it occurs exclusively by a process of diapedesis or escape of the red corpuscles between the intimal cells, without an actual interference with the structural continuity of the vessel wall; still other writers believe that both processes are at work.

My investigations, whilst convincing me that in the initial stages of the escape a process identical to that of diapedesis in other regions is found, have demonstrated that in the later stages of the blood exodus into the surrounding tissues a change of quite a different nature is present. It is dependent on the peculiar structure of the vessel walls, and whilst it is associated with a wholesale opening up of their component parts, it is fundamentally different from rupture, as detected in other places in the body. In describing the results of my investigations it will conduce to clearness to consider first the fine-walled vessels and then those with thicker walls.

Blood Escape from Fine-Walled Vessels

In many places in the premenstrual and the menstrual mucosa the red cells are seen to be leaking into the adjoining tissues between the lining cells of an apparently complete vessel wall (Plate I. and Fig. 7).

In other cases the corpuscles have obviously detached the adjacent cells from one another (Plate I.). It seems certain, however, that in both cases the same process is in operation, namely, that the cells are passing out through gaps in the vessel boundary. In this respect, then, the escape coincides with the process of *diapedesis.* Before the occurrence of the corpuscular escape the surrounding tissues become opened out by the fluid exudate in the manner described (Plate I.). After passing through the wall of an apparently complete vessel, the red cells may stray for a considerable distance into the surrounding stroma. In so doing they may burrow along between the cells or they may lead to a wholesale displacement of the surrounding stroma (Plates I. and III. and Figs. 4 and 7).

In addition to this simple change there is always found another which, at first sight, is of a more complicated nature, and one which, so far as I know, has never been properly described. This consists in the gradual expansion of the small blood lumen into a space of larger diameters, and which, especially towards the surface of the premenstrual and menstrual mucosa, results in the formation of the comparatively enormous blood lacunæ or "distended capillaries" so typically found in this condition. The initial stage consists in a separation of the lining cells from one another. This, as we have noted, is preceded by a similar teasing apart of the surrounding stroma by the œdematous exudate. The spreading apart of the lining cells, at first only sufficient to permit the passage of the red cells, is followed by a complete detachment, the one from the other. The opening out of the adjacent stroma now enables these intimal cells to step back, and we then obtain a blood space apparently destitute of the ordinary flattened lining cells, for in the process of separation these are usually found, as it were, to draw themselves together, and to identify themselves in every respect with the neighbouring stroma elements. In this we see a perfect analogy to the changes which I have described in the stroma cells when they are spread apart by a watery exudate. I have pointed out that under these conditions the cell distinctions disappear. The flattened cells of the basement membrane and the elongated cells scattered through the stroma have lost their differential shape, and are seen to resemble in every detail the typical round or stellate stroma element; so with the flattened intimal cell of the blood-vessel. In some places this vascular change is seen to involve one side of the wall, the other side retaining its usual flattened cells.

The various steps in the process are well brought out in Figs. 2 and

10-12. The changes are also brought out in Plate I. in a manner almost diagrammatic in its clearness. In the small vessel in the lower part of the plate the flattened appearance of the intimal cells is in parts well retained. That this difference between these cells and the adjoining stroma cells is only present in one direction is demonstrated by the fact that where the wall has been cut across tangentially at their level they are seen to be indistinguishable from the stroma elements. Between the lining cells and the stroma cells are seen the same protoplasmic communications as are present between the ordinary tissue cells. At several regions the blood cells have strayed beyond the vessel confines, and there the intimal cells have been carried outwards to range themselves alongside those of the stroma. In the other vessel, at the level of *d*, the same changes are present. The ordinary flattened cells have here been displaced outwards to a greater degree than is present in the other vessel. As is often noticed, a few of them have apparently been left behind in the course of the expansion. This change often progresses to the extent of forming large blood sinuses in the mucosa, situated, as already stated, for the most part towards the surface. In this way are formed the sub-epithelial hæmatomata of Gebhard. The expanded vessel represented in Plate I. is formed in such a way, and it indicates what is often seen, that the expansion is still progressing. Here and there along its wall the blood is seen to be still escaping into the adjoining stroma, and the lining cells are still stepping back to allow of the increase in the diameters. A blood sinus similarly formed is represented on Plate II. Here, as before, the expansion is still seen to be progressing. This figure also indicates that whilst round the greater part of the circumference the wall is formed by ordinary stroma cells, here and there flattened cells are present, identical in every respect with the intima of the resting vessel. A similarly produced blood sinus is shown in Fig. 2.

As already pointed out, when the original intima is opened out the flattened appearance usually becomes dispelled, and the newly-formed blood space seems to be lined by ordinary stroma cells. An appreciation of the steps of the change enables us to understand the rationale of this. We now know that into the constitution of the new wall both the original intimal cells and the adjoining stroma cells have entered, though in many cases it is impossible to tell which was which. As I have already contended, this discovery is amenable to one explanation only, namely that the intima and the stroma cell are structurally and functionally identical. This idea is confirmed by finding that here and

there round the wall of even a large sinus the cells are seen to be flattened like a true endothelium. This is seen on both walls of the large blood space shown in Plate II. If my interpretation of the mode of production of such a space be correct, these flattened cells correspond to stroma elements which have assumed this shape.

These observations also enable us to understand the appearances which would seem to have perplexed other writers. In the literature one occasionally meets, in the course of an account of the mucosa vessels, with a description of vessels which are apparently formed throughout by the stroma elements. So far as I know it has never before been explained. In Fig. 5 are shown two vessels, one conforming with this description, the other with an ordinary flattened intima.

But, it may be urged, are these appearances not due to the fact that in the beginning the flattened intima has been shed, allowing the stroma elements to come into direct contact with the contained blood? In answer to this I may state that I have never seen any evidence of this. On the other hand, it is often possible to see the flattened cells being carried back into the stroma by the escaping blood (Plate I. at *d* and *g*). I have also pointed out that the stroma elements can assume a shape identical with that of the original intima, where they lie immediately against the blood.

It seems to me that the *expansion of the originally small vessel into a sinus-like space is due entirely to a process of displacement. It is initiated by a teasing apart of the intimal cells, followed by a giving way of the surrounding stroma. In its final form the new wall is formed almost entirely of the stroma elements.*

The structural peculiarity of the stroma has now amply justified its existence. The fact that it is composed of a soft, homogeneous, protoplasmic mass allows of the occurrence of the above functional changes with the greatest possible efficiency. *The vascular expansion is no more by a process of rupture than is the displacement produced in a mass of jelly by forcing into it a firmer body.*

The probable explanation of the cause of these changes and their bearing on the mode of formation of the blood cavities in the pregnant mucosa will be discussed on subsequent pages.

Changes in the Thicker-Walled Vessels

Where the vessel wall is supported by a massing of the stroma cells in concentric layers round the intima, the blood escape is naturally

resisted to a greater extent than in the case of the capillary twigs. Here, however, exactly the same teasing asunder of the surrounding cells by the fluid exudate, followed by an escape of the corpuscular elements, is always seen in the menstrual mucosa. After the opening out of the adjacent stroma the circularly disposed media cells are allowed to become stripped off. In the case of the thicker vessels this must, of course, first involve the outer structures, the remaining cells then becoming teased out in successive layers from without inwards. This change sometimes involves the wall uniformly round the entire circumference, in other cases one aspect gives way before the other. In many cases it is possible to see the detachment of the cells in complete layers, which, if the cells are united together by uninterrupted films, must correspond to complete protoplasmic sheets.

With the completion of the detachment of the supporting elements the intimal cells become separated, permitting an escape of the corpuscular elements of the blood. The process now corresponds in every respect to that described above in connection with the capillary vessels. The blood strays out between the lining cells of an apparently complete wall, or, in the process, these cells are carried outwards and, with the surrounding stroma, become increasingly displaced to form the wall of a new blood sinus or lacuna.

In Fig. 18 is represented an appearance frequently detected in the menstrual mucosa. Towards one side the vessel wall is well supported; on the other side there is seen to be a wholesale escape of the red cells into the surrounding stroma. There has obviously been an expansion of this part of the vessel lumen, resulting in a carrying out of the intimal cells alongside the stroma elements, from which they are indistinguishable. This figure indicates that in the blood escape there may be no definitely marked stages in the opening out of the wall; the intima and stroma become uniformly displaced outwards.

The changes just described in connection with the thicker vessels again prove beyond doubt the easily displaceable nature of the structures, and they, in addition, confirm in the strongest possible manner the description I have advanced of the true nature of the stroma. Blood-vessels and surrounding tissue are simply part and parcel of the same soft, nucleated, protoplasmic mass. *This structural peculiarity of the mucosa is obviously designed for the purpose of permitting, with the greatest possible efficiency, an immediate flushing of any part of the stroma with a plentiful supply of blood. If we are to define the true nature of the mucosa in terms of the functional changes which it exhibits, it must be designated,*

not merely a spread out lymph surface such as Leopold named it, but a potential blood sponge. In view of these observations we can now appreciate fully the reason and the necessity of the vascular structure —the presence of any fibrous or elastic tissue in the wall would obviously hamper the occurrence of the ready opening-up which I have described.

The displaceable nature of the stroma tissue, in addition, is obviously devised for the purpose of allowing the ready formation of the blood sinuses which develop in the menstrual mucosa. *Prima facie* it would seem not unlikely that the blood lacunæ, which correspond in conformation to these described, though often reaching a much larger size, that are found in connection with the chief functional activity of the mucosa (pregnancy) would owe their origin to changes similar to these just described. This I shall refer to in a subsequent chapter.

The Factors which Determine the Mucosa Changes in Menstruation

From the middle of last century, with the work of Bischoff, Pouchet, and others, dates the conception that ovulation is of periodical occurrence, and that between it and the changes which the uterine mucous membrane periodically undergoes in association with the menstrual process there exists in some way an interdependence. In 1865 Pflüger first definitely formulated a possible explanation of this relationship. The theory associated with his name supposed that the gradual enlargement of the Graafian follicle led to an increasing stimulation of the nerve fibrils imbedded in the ovary. When this stimulus attained a certain strength it led to the production of a powerful reflex dilatation of the vessels of the internal genitalia associated with the escape of the blood from the uterine mucosa. Although this theory, as first enunciated by Pflüger, has lost the support it used to command, most text-books and most investigators would seem to attribute the chief menstrual changes in the mucosa to a congestive process. The demonstration by Leopold, followed later by many other writers, that during menstruation there may be no evidence of ovulation in the ovaries indicated that the two processes are not necessarily simultaneous, and therefore that ovulation cannot be considered as the immediate causal agent of the menstrual changes. The well-known fact, moreover, that ovulation may occur in the absence of menstruation, as proved by the occurrence of conception before the *menarché* and after the menopause, and during

the amenorrhœa of lactation, indicates, if it does no more, a still further independence of the two processes.

In 1871 Sigismund advanced the idea that menstruation should rather be looked upon as an indication or rather as the result of the failure of conception. The changes which the uterine mucosa periodically exhibits were by him attributed to a preparation of a nest for the ovum, and with a failure of conception the mucosa was separated, somewhat similarly to what occurs during abortion, with the production of the menstrual flow. As he stated, "Die Menstruation ist mithin ein Abortus." According to this theory ovulation precedes menstruation by some time, and, in the case of pregnancy, the fertilised ovum corresponds to the ovulation period associated with the first monthly flow missed. Sigismund's theory received the support of Löwenhardt, Aveling, Löwenthal, and others. The more recent researches into the microscopic changes of the mucosa during menstruation, by demonstrating the absence of a shedding such as found during abortion, must be considered to cripple seriously, if not actually to invalidate, this theory.

Although the existence of a relationship between the ovaries and the menstrual function had for long been foreshadowed by scientific workers, it was not until comparatively recent times that this dependence was clearly and indisputably established. With the introduction of, and the extension of, the operative procedures on the genital tract, it has now been amply demonstrated that the removal of the ovaries is associated with an abolition of the menstrual function. In many cases, after an apparently complete removal of the ovaries, menstruation may continue and this, at first sight, might tend to controvert the above statement. The well-demonstrated fact, however, that even the smallest portion of ovary left behind may suffice to retain the menstrual function would amply explain these apparently anomalous cases. The fact that, after the production of an artificial menopause by the removal of the ovaries, the uterus usually shrinks and atrophies (a statement amply borne out by recent experiments on animals) indicates that the ovaries exert in some way over the uterus a general trophic influence, and are essential for its general nutrition. In the absence of this constant influence the atrophy which it undergoes leads to a falling into abeyance of its functions.

Substantial confirmation of these statements is found in the results of transplantation of ovarian tissue. Morris, Glass, and others have reported cases of women in whom menstruation, which had been suspended

by a removal of both ovaries, reappeared after they had transplanted ovarian tissue derived from other patients. Morris, Cramer, and others have likewise shown that a failure of menstruation, due to an atrophic state of the ovaries, may be overcome by the transplantation of healthy ovarian tissue. The experiments of Halban, Knauer and Marshall and Jolly on the lower animals coincide with the results just mentioned in the human subject. Pro-œstrum, followed by œstrus, can be restored to animals, whose ovaries have been removed, by transplanting ovarian tissue obtained from other animals.

The exact nature of the ovarian influence still awaits solution, but by most workers nowadays it is attributed to some chemical secretion or hormone passed into the blood stream, by which not only the uterus but the general functions of the being are maintained at their proper level. This conception thus endows the ovary with a function apart from that of ovulation, and brings it into line with the ductless glands of the body (the islets of Langerhans in the pancreas, the suprarenals, the thyroid, the pituitary, etc.). Fraenkel, of recent times, developing and elaborating an idea which he attributes to Born, has suggested that this internal secretion, which is directly concerned with the changes in menstruation and pregnancy, is provided by the cells of the corpus luteum. In experiments conducted in animals he showed that, if the corpus luteum be destroyed by the galvano-cautery immediately after the ovum is fertilised, it does not enter the uterus; if destroyed soon after it has become engrafted, it is shed. Destruction of the corpora lutea leads to a uterine atrophy. He thinks that the corpus luteum is necessary for the production of the hyperæmia of pregnancy. If the ovum does not develop, the vascular changes result in the menstrual flow. He tested these experimental results on patients in whom the abdomen had to be opened for some surgical complaint. In nine the developing corpus luteum was destroyed; in five the menstrual flow was delayed beyond its expected time for periods varying from three to eight weeks; in three there was slight bleeding after the operation, such as is often met with after an abdominal operation, but the menstrual flow was delayed for eight weeks; in only one case was menstruation unaffected. This interesting theory is being widely tested, with results which seem on the whole to indicate the limitation of its claims.

The fact, for example, that ovulation occurs only during œstrus in many mammals, when there are often no corpora lutea present (the preceding œstrus may be many months before), would tend to invalidate one part of the theory. That the corpus luteum, however, is necessary

for the early imbedding of the ovum is supported by the experiments of Marshall and Jolly, and of Blair Bell on the lower animals. This influence is essential, in all probability, only for the first few days. In the human subject, as also in animals, the extirpation of both ovaries may leave the pregnancy unaffected if the operation is performed at a later period.

The following statement may be fairly held to summarise the orthodox conception regarding the factors responsible for the menstrual changes in the endometrium:—The ovary (the exact portion of this is unsettled) elaborates an internal secretion or hormone which periodically passes into the blood circulation. This leads to a congestion of the uterine mucosa, with, in the premenstrual stage, a marked swelling due to œdema, hæmorrhage, etc., and in the next stage to an escape of the blood into the uterine cavity. The idea that a fatty degeneration of the tissues is the cause of the blood exit is now untenable.

From what has been said on previous pages it will be understood that the exodus of the red cells through the vessel precincts is intimately associated with the œdematous escape from the vessels. The corpuscular exit can in many cases be seen to occur after the opening out of the cells of the media and the production of gaps in the intima of sufficient size to accommodate the red cells; in other words, that the process occurs after the preliminary infiltration and loosening of the stroma protoplasm by means of the serous exudate. As I have pointed out in several places, the converse of this statement is untrue, namely, that an œdematous infiltration is necessarily associated with a blood escape into the affected tissue. One not infrequently finds an extreme watery loosening of the stroma without an escape of the red cells, and even where the lining cells of the vessel are seemingly so opened apart as to accommodate between them one or more red cells. Under these circumstances the vessels are often seen to be engorged with the red corpuscles which may actually lie right up against the vessel boundary. This I have shown to occur even when the vessel wall is formed clearly by the ordinary stroma elements, and I have adduced from this that the cells are not, as usually stated, merely united by protoplasmic fibrils, but that, under ordinary circumstances, they are connected by complete, though thin, films of protoplasm, the giving way of which is usually essential for the leakage of the red cells. The preceding watery escape has occurred through this fine sheet in a manner to be presently described.

The fact that the escape of the fluid constituent of the blood precedes and in fact prepares the way for, the subsequent corpuscular exodus indicates that any investigation which casts light on the former process will go far to elucidate the problems associated with the latter.

Factors Determining the Fluid Escape from the Vessels

In conducting an inquiry into the etiological factors responsible for an increased transference from vessel lumen to tissue spaces in the uterus, we are brought up against many investigations of a similar nature which have been carried out by other observers for the purpose of elucidating the agents which determine an œdematous escape in other regions. These investigations have been for the most part experimental in nature, and in most cases have been carried out on the assumption that the changes which determine the increased fluid escape that constitutes œdema are similar in nature with the physiological changes that ordinarily dominate the process of lymph formation. In the case of œdema these factors have remained the same, but they have become altered in the direction of an increase. With these possible factors must be included any condition leading to an obstruction of the normal lymph flow. This, it is obvious, may lead to an accumulation in the tissues of lymph which, though normally produced, collects in excessive amount. The justification of thus arguing from one condition to the other is seen to be complete when we remember that in the former inquiry all the possible factors responsible for the fluid transference must be included.

In the first place it is easy to dispose of the last of the factors enumerated above, namely a lymphatic obstruction, as the direct cause of the fluid accumulation in the tissues. The justice of this will become evident in the course of this record. Suffice it for the moment to state that in the changes I believe we have sufficient evidence to prove beyond doubt that there is some process leading to an *increased escape* from vessel to tissue.

The theories advanced to explain the variations in the amount of fluid held by the tissues in physiological and pathological states fall into one or other of two headings, according as they are (1) physical or chemico-physical, or (2) vital.

(1) *The Physical or Chemico-Physical Theories.*—The oldest explanation is associated with the name of Ludwig and his disciples. According to them an increased fluid transference across the vessel walls is due to

a mechanical squeezing of water across the wall from the lumen, where the pressure is higher, to the tissues, where it is lower. This may be called the *mechanical or filtration explanation.* Most recent workers on the subject hold that, in addition to this factor, to explain the phenomena it is necessary to invoke the existence of alterations in the tissues which determine an active dragging or imbibition of the fluid from the vessels. It is impossible in this place to review in detail the varying ideas held. For this see the Appendix. By some investigators who have been influenced by the work of the plant physiologists, especially Pfeffer and de Vries, the laws of *diffusion and osmosis* are supposed to afford an ample explanation. A liberation of crystalloidal elements in the protoplasm and spaces of the tissues is supposed to raise the osmotic tension of the tissues. So long as there are colloidal membranes present, this change will result in a diffusion of the fluid from the vessels in an outward direction in an endeavour to readjust the osmotic pressure discrepancy. By these writers the crystalloids are set free by the normal activity of, or by pathological changes in, the colloidal elements of the tissue protoplasm. Whilst these investigations marked a distinct advance in the study of œdema production, it would seem from recent work that they fail to account for many of the phenomena. In the first place, in most animal cells it is impossible to detect the existence of a cell membrane similar to that in plant cells, and essential to an explanation based on osmotic laws. It is known, moreover, that if the cell contents are squeezed out into a solution they behave exactly the same as the original cells. On purely osmotic laws, in addition, it is difficult to account for the continual escape of dissolved matter from the cell which must be going on during its activities, and for the continual absorption of dissolved substances from the surrounding medium which are necessary for its nourishment. It has been proved, also, that cells behave differently with solutions of different substances having the same osmotic pressure. Whilst these facts prove that osmosis and diffusion fail to embrace all the many changes which the cell protoplasm exhibits in relation to its environment, and especially to its behaviour towards water and substances dissolved therein, it is nevertheless likely that these physical processes are intimately bound up with certain of these alterations. The investigations which I shall describe would suggest the existence of a fluid absorption in a way which in its results, at any rate, is similar to that which osmotic changes would produce.

Recent experiments would tend to indicate that whilst the chemical

constitution of protoplasm, especially in regard to its water-holding powers, is of tantamount importance in this connection, the imbibition and the liberation of the water follow laws somewhat different from that of mere osmotic diffusion across a defined colloidal membrane. "The whole chemical structure of the cell and that part of it which is physiologically active is the osmotic machine, and needs no membrane permeable or impermeable in order to exhibit the usual osmotic phenomena of shrinking or swelling, leading finally to disruption. . . . In all cases the nature of the bioplasm is so differentiated chemically as to form a dividing surface readily permeable to the solvent, and this is all that is required, in addition to the varying unions or holding powers between the cell colloids and crystalloids, to establish an osmotic cell. As an example of what is meant here, we may instance the swelling of fibrin, connective tissue, and gelatine under the imbibition of water. Between gelatine and water there is no structural membrane with semi-permeable pores, yet the gelatine takes in water in a truly osmotic fashion, and the pressure developed, if the swelling and uptake of water are resisted, is very high." (Moore*). Other writers (Fischer† especially) refuse to see in the fluid imbibition of fibrin, gelatine, muscle, etc., an osmotic phenomenon. Fischer believes that the process of œdema depends entirely on the water-attracting and water-holding powers of the colloids of the protoplasm, and that this cannot be called an osmotic condition. It will be seen, however, that these two explanations differ not so much in substance as in terminology. (See Appendix.)

According to the chemico-physical explanations, then, an œdema is due to any condition which, in the presence of water, increases the affinity of the tissue colloids for water above the normal standard. This increased affinity is due either to the production of colloids with a greater water-holding power or to the production of crystalloids.

(2) *The Vital Theory*, associated especially with the name of Heidenhain, explains an increased water transference across a vessel wall as due to a selective or vital secretory activity on the part of the endothelial cells.

In describing the results of my investigations into the changes responsible for the increased fluid accumulation in the premenstrual and the menstrual mucosa, I shall describe, in the first place, the process as demonstrated in the case of abnormally thick vessels, and in the second

* Moore.—"The Equilibrium of Colloid and Crystalloid in Living Cells," *Further Advances in Physiology*. Arnold, 1909.

† Fischer.—"Œdema," *Trans. Coll. Phys., Philadelphia*, 1909.

place, as it is manifested in the normal vessels and stroma. This plan I intend to adopt merely for the sake of greater lucidity. As will be subsequently indicated, the actual changes are often obscured in the case of the normal mucosa. This fact, I believe, explains the frank admission by many observers of their inability to correctly decipher the factors in operation. In the case of abnormally thickened vessels, whose walls, as it were, resist the fluid escape, the changes, on the other hand, are forced into prominence. For this reason, and in view of the fact that this research, I believe, breaks new ground, I have thought it wise to commence with the obvious and thence to pass to the less clear.

Mode of Production of Œdema, as seen with Thick-Walled Vessels

The observations to be recorded were carried out in a menstruating uterus removed by vaginal hysterectomy from a patient of forty-two who had suffered from severe and protracted menstrual periods for many years. Every form of treatment, including curettage, had been tried without avail. The usual course in these cases was adopted, and the uterus was removed. This was done on the sixth day of a protracted period. After removal the specimen was almost immediately plunged in Pick's Solution (No 1) for hardening. The preservation is excellent.

In the stroma and in the vessels changes of a nature similar to those present in the ordinary menstrual mucosa were seen. The mucous membrane was markedly thickened and softened, these changes extending throughout the entire extent of the uterine body. The microscopic alterations in structure are similar in nature, though in an exaggerated degree, to those seen in the normal menstruating mucous membrane. The superficial part of the stroma, especially, is markedly œdematous and is infiltrated with blood. With the exception of a shedding of the superficial epithelium in parts there is no evidence of tissue destruction. The glands are markedly dilated, in some places forming cyst-like dilatations in their course.

The blood escape from the vessels is found to have occurred exactly as described in the preceding section with regard to the processes at work in normal menstruation. There is the same teasing out of the stroma and the vessel walls by an œdematous escape, followed by a wholesale exodus of the red cells. Here again the change is most evident towards the surface. Throughout the stroma, even towards the surface, a large number of vessels are seen with walls thicker and more condensed than are ever found in the normal mucosa (Figs. 14 and 15). It is in these

vessels especially that we find important information regarding the mode in which the œdematous escape has occurred in this abnormal specimen.

The unusual thickness of the vessel coats is due to a marked condensation of the surrounding stroma. Immediately external to the intima the cells are closely packed together, forming a deeply staining mass rich in nuclei. The stroma external to this is often arranged in concentric layers round the vessel (Fig. 14). We thus see that the great difference between these vessels and those of the healthy mucosa is found in the packing together of the cells to form the pathological media. As I shall point out, this is not to be considered as in any way analogous to the media of similarly thick vessels in other organs, for under certain circumstances the cells can open up just as I have described in the normal vessels, and we then see that they apparently correspond in every detail to stroma cells.

In Figs. 14, 15, and 17 are represented vessels whose walls are teased out by fluid tracks that extend into the adjacent tissues, where they usually expand into large clear territories, because of the more easily displaceable nature of the stroma. In Fig. 15 this appearance is shown; the remarkable change present is due to a wholesale gap in the outer, less supported portion of the vascular wall, which gives the impression that it had been forcibly excavated. In Figs. 14 and 17 the same condition is present. These conditions are obviously due to the fact that the thick vessel walls have resisted the œdematous outpouring, except in certain regions, where they are less firmly knit together. At first sight the giving way would seem to be readily explained by mechanical means, *i.e.* increased intravascular pressure resulting in a filtration of fluid through the vessel wall, with a displacement of the surrounding unsupported stroma and then of the outer layers of the vessel. Whatever be the cause it is clear that, to induce the marked displacement evident in many of the vessels, it must correspond to a comparatively great pressure.

A careful scrutiny of the histological appearances present demonstrates with certainty that the fluid cannot be escaping from the vessels in response to merely mechanical influences. There is some influence of a more complex nature than a mere squeezing or filtration from the blood-vessel into the tissues. In the first place, in many cases it is possible to detect that, separating the vessel lumen from the œdematous track ploughing up the wall, there is nothing but a very fine, though

complete, pellicle of cell protoplasm (Figs. 14 and 15). *It seems to me that a mechanical force sufficient to detach the cells of the markedly condensed wall in the wholesale manner in which the process is obviously occurring would result in an immediate rupture of the very attenuated protoplasmic bridge to which I have referred.* It would seem certain from the appearances that the hydrostatic pressure on the immediately outer aspect of the pellicle must be, at any rate, not appreciably lower than that in the vessel lumen. If this actually were the case, nothing could save it from immediate rupture. This appearance is often present, and indicates that, to explain the phenomena, we have to invoke some influence other than a mere mechanical transudation of fluid.

Another fact of importance is found in the observation that *the fluid in the immediately adjacent portion of the vessel wall has accumulated under a hydrostatic pressure actually higher than that present in the vessel lumen.* This is clearly indicated by the appearances present in the majority of the vessels. In Fig. 16, which is a drawing under higher magnification of the lower part of the vessel represented in Fig. 15, it is seen that on the left side the collection of the fluid in the inner part of the vessel wall has actually resulted in a bulging of the affected portion into the cavity. The fluid spaces in and between the cells have swollen the corresponding region inwards. On the right side of the same vessel, at its lower part, the same condition is present. Above this it is again seen, and here it has been associated with a more profuse fluid exodus into the adjoining tissue, which in the process has been extensively teased out.

It seems to me that these observations prove that the fluid, which is leaking through the vessel wall, is entering the tissues under the influence of some force other than a mere mechanical filtration from vessel lumen. If such is the case, what other factors can be called in to explain the phenomena? A reference to the formula comprising all the possible agents which I have inserted at the beginning of this discussion discloses the fact that we are left in our search to changes in the intimal cells of an active secretory nature and changes in the tissues as a whole.

The Rôle of the Intimal Cells

In practically all the thick-walled vessels exhibiting the œdematous opening out of their walls there are present important alterations in the intimal cells—alterations which might, at first sight, suggest that the fluid transmission from vessel to tissue is occurring by a process of

vital or secretory activity. At the outset I would submit that it seems unlikely that a secretory activity, whatever this may mean in terms of physical and chemical cellular changes, on the part of the lining cells would, of itself, suffice to explain the drastic vascular and tissue displacement present. I would advance as logical the opinion that an active change of such a nature cannot account for the wholesale opening up of the thick and dense vessel wall and the adjacent tissues external to the intima; and, in support of this, I would call attention to an appearance already advanced as contra-indicative of a purely mechanical or filtration explanation. A glance at Fig. 14 shows that the fluid track on one side of the vessel wall is broken by fine tissue bridges or films; it seems likely that an active passage of fluid across the intimal layer so powerful as to tease out the wall to the degree present would inevitably break down the fine tissue partitions interposed in its path. On the other hand, the persistence of these very films I shall indicate in the ensuing paragraphs is amply accounted for, and, in fact, is only explained by, the introduction of a factor other than a filtration or a local intimal activity. Their presence is more than a coincidence—it is intimately bound up with the tissue changes which dominate the whole process.

In Figs. 15, 16 and 17 are shown the changes in the intimal layer to which I have referred. The cells have been markedly swollen and projected into the vessel lumen by the collection in their substance of a clear fluid. In some instances the appearance somewhat suggests that associated with an intracellular fatty degeneration. That it is not so is at once proved by preparing and staining the sections in the appropriate manner. The changes are without doubt due to an accumulation within the cells of fluid abstracted from the vessel lumen, and which has collected in the cells under a hydrostatic tension in excess of that present in the blood channel. It must be dependent on some protoplasmic alteration leading to an active fluid imbibition. Although with regard to the exact nature of the chemical changes involved in such a cellular alteration, which has been frequently noted in other regions of the body, scientific workers are still in ignorance, on some aspects of the subject there is a unanimity. Whilst the secret of the inner changes still awaits elucidation, we are enabled, thanks to experimental research, to account for the results in a manner which leaves little room for uncertainty. The vacuolar changes in the intimal cells are, as the figures show, associated with a displacement of the nucleus and cell substance to the periphery by the accumulating fluid.

In many instances the swollen cells project like blebs, often massed together, into the vessel, whose lumen may be distinctly encroached upon in the process. In other cases the swollen cells stand out as elongated bodies or as isolated beads set into the inner vessel wall. *These appearances demonstrate beyond doubt that all along the inner aspect of the vessel walls there are present cellular changes which have determined an active imbibition of fluid from the blood.*

The Rôle of the Stroma Protoplasm

What bearing have these observations on the mode of production of the diffuse œdematous infiltration of the surrounding vessel walls and stroma? If the opinions advanced in a preceding section of this research be correct, that in the uterine stroma we have a collection of poorly differentiated cells, all of which, intimal as well as ordinary stroma cell, are structurally, and, apart from the accident of location, functionally identical, it would seem not unlikely that in the above changes we are getting near an explanation of the diffuse fluid escape. Whatever be the original cause of the changes in the intima, it would seem likely that this cause will act similarly on the cells of the vessel wall and the adjacent stroma, and that in this way there would be set into action diffuse tissue changes culminating in a widespread *absorption* of fluid from the blood-vessels. If we can discover changes in the stroma elements similar to those detected in the intima, not only do we advance far in connection with our quest, but we are able to indicate that the intimal alterations are to be considered more as an incident in, than as a cause of, the increased fluid escape; in other words, that there is nothing to favour the recognition of a local secretory activity on the part of the lining cells.

The changes present in the vascular walls and in the stroma strongly suggest that in these regions the œdematous accumulation has occurred in consequence of tissue changes identical with those evident in the intimal layer. The situation of the cells in the latter situation has, of course, forced the process at work into prominence, and has thus enabled it to be deciphered with comparative ease. In Fig. 16 it will be noted that in the vessel wall the fluid accumulation is associated with tissue changes identical with that present in the immediately internal lining cell. As in the case of the intima, the fluid has collected in distinct vacuoles in the cell protoplasm, which has been displaced to the periphery as a fine layer, separating the one fluid space from that in the immediate neighbourhood. It is seen that

the fluid track is for this reason not complete, but is interrupted by a number of these fine films. This appearance, as I have pointed out, is amenable neither to a mechanical explanation of the fluid exit nor to a local activity of the intimal cells. If both of these explanations fail we are again left to tissue alterations which have determined an active dragging of the fluid into the opened-out regions. I would submit, then, that *to explain the œdematous accumulation in the vessel wall, as in the intimal cells, we have perforce to recognise the existence of changes associated with the liberation of elements with a greater affinity for water than has the resting protoplasm.*

It is thus seen that the œdematous teasing out of the endometrial tissues in this condition is due to the presence of alterations in the cell protoplasm of the structures from intima to stroma. The enhanced affinity for water has resulted in a streaming outwards of the fluid from vessel lumen to tissue. Of the presence of this increased attraction for water the cellular changes provide direct evidence in the case of the intima. In the case of the stroma the evidence is, so far, chiefly circumstantial. In the next section this will be reinforced by evidence of a direct nature. The intimal changes are determined by the resistance which the thickened walls offer to the fluid escape. This is clearly proven by the fact that with the opening out of the vessel wall the intimal bulging becomes less, and that ultimately, with a complete teasing asunder of the vessel confines, the intimal elements collapse altogether (Figs. 16 and 17).

Mode of Escape of Red Blood Corpuscles

In all the vessels in this specimen from which the blood corpuscles are escaping the exodus is only occurring at that part of the wall which is completely opened from intima to stroma (Fig. 17). In the case of the fine vessels this is easy, and there is accordingly an extensive capillary hæmorrhage going on in a way exactly like what occurs in the normal menstruating mucosa.

What factors determine the corpuscular escape from the opened-out vessel? In view of what I have said it would seem certain that the continual fluid stream from vessel lumen to stroma in the manner described must carry out the corpuscles into the stroma as far as there is a complete continuity of the track. As the stream of fluid must be in force not inconsiderable, this of itself would seem amply to account for the hæmorrhage, although it must be remembered that, subsequent to the opening out of the wall, the ordinary intravascular blood-pressure

may take a share in the changes. The intravascular blood-pressure dependent on the *vis a tergo* must, as the result of the continual dragging forward of the fluid by the tissues, in these conditions be considerably supplemented.

Causation of Excessive Uterine Hæmorrhage as Revealed in this Specimen

Before passing on to discuss the cause of the œdematous and blood escape in the normal menstrual mucosa, a few words must be said regarding the light which the above observations throw on the obscure problem of menorrhagia. In the next section I hope to indicate that the cause of the œdema and hæmorrhage in the normal mucosa is due to factors identical in nature with, and differing only in the degree of their activity from, those operating in this abnormal specimen. If this be the case it would contribute additional support to the widely entertained idea that in many cases of menorrhagia, and probably also of metrorrhagia, we are dealing with an abnormal activity of the ovarian influence.

Apart from the similarity of the tissue changes present in the two conditions which I mention here in anticipation for the purpose of completing this section, there are other considerations which render it improbable that in the excessive bleeding in the mucosa in the case just described we are dealing with an influence fundamentally different from that normally acting. In the first place the bleeding merely consists in an increase in the quantity of the menstrual loss and an extension of the duration of the menstrual flow. This would suggest that the same factor is operating, modified either in the direction of an increased activity or by some uterine changes which render the tissues more susceptible to its action. Which of these two different factors is responsible for the pathological hæmorrhage it is impossible to say with certainty. It would seem unlikely that it can be due merely to the vascular thickening, for we have seen that, so far from increasing the tendency to the œdematous and blood escape, this change has actually tended to prevent their occurrence. In view of this, it would seem to me that we are entitled to assume either that the vascular thickening is a coincidence, or, what is much more probable, that it is the result of the influence responsible for the other pathological conditions, *i.e.* excessive œdema, bleeding, and glandular distension. If this is so, it would seem not unlikely that in this specimen we see the results of an excessive activity of the influence which normally is

associated with the four or five days' moderate flow of blood from the uterus.

MODE OF FLUID ESCAPE IN NORMAL MENSTRUATING MUCOSA

I have repeatedly referred to the fact that the vessel walls in the normal mucosa are so formed as to allow of an easy and immediate opening up of their structures by the œdematous exudate which precedes the corpuscular escape. In the last section it was shown how the abnormal condensation of the stroma forming the wall has forced into prominence the exact manner in which the fluid is being passed out. We have there seen that the tissues are actively dragging out the fluid, and are not merely playing a passive rôle such as all previously advanced explanations demand. I have also shown how, immediately after the fluid exodus culminates in a free gaping of the vessel wall, the signs of this active tissue change are apt to become obscured, at any rate on the inner aspect of the vessel. It is thus obvious that, if the same process is being enacted in the normal stroma, the peculiar structural arrangements present here will tend to veil the exact stages of the change; and this I believe explains why the real nature of the process has hitherto evaded detection. When the intercellular spaces become enlarged, and the cells are widely separated, it is often difficult to determine that this has occurred in any way but by a mechanical leakage of fluid into the tissues.

A careful scrutiny of the structural changes in the vessels and stroma associated with the menstrual condition has, however, convinced me that exactly the same process is operating as in the last case, that the fluid exudate, and therefore also the hæmorrhagic escape, are taking place, not by a mechanical squeezing of the blood from vessel to tissue, but that the fundamental cause is to be found in alterations that determine an active fluid imbibition by the tissues of the vessel wall and stroma.

On Plate III. is represented an appearance frequently detected in the menstruating and the premenstrual mucosa. The specimen from which this drawing was made corresponds to the premenstrual condition. It will be noted that there is a marked œdematous opening out of the tissues. The appearance that I wish particularly to call attention to is the extraordinary tissue change associated with the fluid escape. The typical appearance of

the stroma in the shape of more or less well-formed cells united by comparatively simple protoplasmic processes has become completely modified. Instead of the comparatively small number of large fluid spaces, the protoplasm is beset with a multitude of spaces which in some cases are so infinitely small as to be just recognisable with this high magnification (× 1000), whilst in other places they attain dimensions as large as, or larger than, the ordinary intercellular space. The same changes are present in Plate IV. It will be noted that the change has involved the protoplasm uniformly throughout; it has obviously led to a breaking up of the comparatively thick protoplasmic communications which, in the resting mucosa, pass between the cells into the fine fluid spaces separated by the greatly attenuated cytoplasmic walls; it has also involved the perinuclear cell protoplasm often to a like degree. The usual mass of cell substance enclosing the nucleus is often completely replaced by an infinite number of fluid spaces each bounded by the displaced and finely-drawn-out cytoplasm of the original cell body. It is clear that the formation of the fluid spaces in the cell body and in the connecting protoplasm is associated with a marked increase in the bulk of the affected tissues.

The appearances thus revealed are clearly amenable to one explanation, and to one explanation only. *They must be due to alterations in the cytoplasmic composition leading to an active fluid imbibition.* A mechanical increase in pressure in the intercellular space might lead to a wholesale displacement of the cell body, or of the protoplasmic connections, but it could never induce the changes described. While the exact nature of the chemical alterations is still beyond our grasp, we are left in no doubt regarding the results they produce. I have already described changes of a similar kind in connection with the menorrhagic mucosa, and whilst in the last section I intentionally devoted more attention to the changes located in the vessel wall, I may state here that changes identical with those I have described in the normal mucosa were detected in the pathological stroma. In the immediate vicinity of the vessel lumen the protoplasm exhibits changes in every respect similar to those just described. Here the cell substance is broken up by the imbibed fluid which has accumulated in isolated spaces of greatly varying size. Here, again, as in the last specimen, it is often seen that *the spaces immediately abutting on the blood cavity are distinctly swollen inwards, proving beyond doubt not only that the intravascular blood tension is not the factor responsible for the fluid*

escape by a mechanical filtration, but that, so far from this being so, the fluid has actually accumulated in the tissue under a pressure hydrostatically greater than that in the vessel lumen (Plates III. and IV.).

I may state that I have been able to recognise these changes in all my specimens of the normal premenstrual and the menstrual mucosa. They, I maintain, demonstrate beyond doubt that the orthodox conception entertained regarding the mode of the œdematous (and as I shall subsequently point out of the hæmorrhagic) escape must be completely modified. I may state, also, that an examination of several hundred specimens of the mucosa (obtained fresh by curettage) has convinced me that the same tissue changes are responsible for many of the deviations of the stroma from the normal present under pathological circumstances. I have already referred to the changes in menorrhagia. I hope in a future publication to indicate the existence of similar factors in cases of metrorrhagia and leucorrhœa.

The Nature of the So-called Tissue Network of the Stroma and the True Interpretation of the Intercellular Spaces

As was pointed out in the chapter devoted to the more general structure of the uterine stroma, varying ideas have been entertained by different writers regarding the exact structure of the finely-drawn-out threads often seen in the mucosa, and which frequently appear to be interlaced together to form an intricate network. By Leopold this was supposed to be due to the presence of a fibrous connective tissue structurally independent of the cells. More recent research has proved the fallacy of Leopold's observations, and it has now been definitely shown that the protoplasmic processes are continuous with, and are composed of the same material as, the cell bodies.

It seems to me that the researches recorded in the preceding pages mark a still further advance in our knowledge of the intimate structure of the stroma. I have already pointed out that this must be considered to be composed throughout its entire extent of a homogeneous, soft, easily displaced protoplasm. I have further adduced evidence in favour of the idea that the intercellular spaces are not, as is usually held, freely intercommunicating, but consist, in the ordinary resting state, for the greater part each of a fluid cavity completely walled in on every side. The protoplasmic bridges between the cells are not, as they at first sight appear to be, cytoplasmic filaments, but they are complete, though fine, films. It seems to me that the observations described in the last section lend additional support to this view, and

they besides indicate that the many and varying appearances detected in the so-called "network" correspond to the functional changes for which the stroma protoplasm is especially adapted. These appearances are not merely incidental, but are of profound importance from the point of view of a proper understanding of the changes in menstruation and, as I shall subsequently show, in pregnancy.

Enough, I think, has been said in the preceding pages to prove that the network of previous writers in reality corresponds to the spaces in the protoplasm with their thinly-drawn-out but complete envelope of cytoplasm enclosing the fluid which has been actively imbibed. The presence of this complete shell of cell substance was an absolute certainty in the case of the swollen intimal elements of the thickened vessels. In the same vessels it was present in the case of the fluid vacuoles in the inner aspect of the walls, which were seen to project into the lumen. It is obviously present in the case of the vessels represented in Plates III. and IV., where the bulging fluid vacuoles are richly scattered along the inner aspect of the vessel wall. The manner in which the cell protoplasm of the stroma swells up with the imbibed fluid, often to many times its original size, indicates beyond doubt that the water absorbed is contained within complete films of cytoplasm. *These appearances thus prove beyond cavil that the so-called network formed by interlacing threads of cell protoplasm in reality corresponds to an agglomeration in the cytoplasm of fluid which has been actively imbibed, and which is contained in spaces separated by complete walls. The attenuated portions of protoplasm are films and not filaments.* By a disappearance of the films larger spaces are produced. This process may eventually lead to the formation of large fluid-containing areas.

The fact that the protoplasmic changes during menstruation are found to be exhibited in an identical manner by all the different elements of the stroma (intima, media, etc.) is confirmatory evidence of the strongest kind in favour of the interpretation of the structure of the stroma which I have previously advanced. The lining and supporting cells of the vessels were seen to be *structurally* similar to the stroma elements. They are now seen to be *functionally* identical.

The above observations lend added favour to the idea previously advanced, that the intercellular spaces of the resting state correspond to fluid vacuoles, each completely shut in. In proof of this it was pointed out that as a rule in section the spaces are seen to be completely encircled by the fine protoplasmic bridges, and that where the opened-out stroma cells take part in the formation of the wall of an expanded

vessel, the red corpuscles are often perfectly retained. The same phenomenon is often seen where the red cells are being drawn into the stroma tissues; they are often seen to extend just so far as such a completely walled-in space.

These observations, it seems to me, force us to the conclusion that the structure of the stroma, consisting as it does of a homogeneous and easily displaceable protoplasmic surface, is especially devised for the free play of the forces which determine a fluid transference from vessel lumen to tissue.

While it seems to me likely that the description of the structure of the mucosa which I have given applies, in the main, to every part of the mucosa, I am unable to make any definite statements regarding the presence or absence of any continuous lymph channels. All I do claim is that the orthodox conception of the intercellular spaces, in view of my observations, demands serious modification. Whether or not some few of these spaces differ from their neighbours in being united together to form a continuous lymph track I can neither assert nor deny. In the course of my investigations I have never seen any appearances to suggest the existence of such lymph vessels.

Explanation of the Hæmorrhage into the Stroma during Menstruation

We have seen that the fluid constituent of the blood is sucked into the tissues in response to a universal increase in the affinity for water of the stroma protoplasm. This change precedes the corpuscular escape. By it the stroma cells and the walls of the vessels are teased apart, in this manner preparing the way for the exit of the red cells.

It has been shown how the escaping fluid is able with ease to displace the soft stroma protoplasm, in which it collects in vacuoles of varying sizes. The extraordinary facility with which this displacement occurs would seem to warrant the conclusion that the consistence of the protoplasm is somewhat of the order of a soft jelly.

In view of these facts it is not difficult to understand how the continual and, in all probability, comparatively powerful stream of fluid passing from vessel to tissue should lead to a dragging out of the red cells. Of one thing, however, we may be certain, that whereas the fluid may diffuse freely across a protoplasmic sheet, for the leakage of the red cells a complete gap is essential. This fact has been repeatedly borne in upon me in the course of my investigations. It is sometimes seen, for instance, that the red cells are held back, while the fluid is obviously freely leaking, by such a fine film as passes between two cells.

These facts clearly explain how in the premenstrual phase there may be an extensive œdema with little or no hæmorrhage.

I have pointed out how, by a disappearance of the cytoplasmic partitions, there may be an amalgamation of adjacent fluid spaces. This may be due to a mere mechanical giving way, or it may be due to a fluid imbibition by, and solution of, the pellicle of protoplasm. By the fusion or expansion of the spaces large clear territories may result. This ready detachment of the sheets (again determined by the consistence of the protoplasm) will amply account for the corpuscular escape. Whether the cells can only pass along continuous tracks previously prepared for them by the fluid accumulation it is impossible to say with certainty. It seems to me, however, more than likely that if the fluid stream from one side to the other of a protoplasmic film be appreciable, any red cell carried up against it will tend to pass across. This may cause an immediate and complete giving way of the whole film, or, what is not unlikely in view of the previous investigations, the gap may again close up by a flowing together of the protoplasm.

In any case it seems certain that *the direct cause of the hæmorrhagic escape is the stream of fluid created from vessel to tissue by the active stroma changes.*

Explanation of the Formation of Blood Lacunæ in Menstruating Mucosa

In view of these observations it is not difficult to understand the manner in which the comparatively large blood lakes or "distended capillaries," the exact structure of which I have described in detail (Plate I.), are formed in the premenstrual and the menstrual mucosa. It would seem at first sight not improbable that they are formed as the result of the constant and widespread imbibition of fluid in the superficial regions of the mucosa. This, it is clear, must determine an increased flow of blood along the vessels behind. That this explanation, however, does not account for the formation of these lacunæ is proved by finding them in the most superficial regions of the stroma. We have already indicated that the mechanical influence of the intravascular pressure does not account for the passage of the fluid from the vessels that opens up the surrounding stroma. The same considerations that warranted this conclusion would seem to apply to the vascular expansion. As in the case of the active fluid imbibition, the cause of the expansion at any point would seem to be dependent on local tissue changes. I have pointed out that the opening of the wall at any particular site in an

enlarging vessel is due to a disappearance of the protoplasmic film separating the lumen from the immediately adjacent tissue space. How does this occur? It seems to me likely that it takes place in a manner represented in Plate II. Here the vessel is still small, but it is obviously in the process of expansion. This is determined by a bulging and *giving way of the corresponding tissue film towards the lumen.* This immediately carries the lumen a degree farther out. The same process, by involving the entire circumference of the small vessel, will result in a new and expanded wall, in which the stroma cells are included. So the change will go on until a large sinus is produced. These considerations suggest that the expansion is due to the same tissue changes to which I have repeatedly called attention. In a subsequent section I shall demonstrate exactly the same process in the wall of the pregnant tube.

Rôle of the Epithelium in Determining the Changes Present

As has been repeatedly pointed out by other observers, the œdema and hæmorrhage during menstruation is often localised in a remarkable manner to the neighbourhood of the surface epithelium or glands. Under the lining epithelium the extravasated blood often collects either in the form of a continuous sheet or of little hæmatomata.

The explanation of these phenomena is not difficult to find when it is remembered that during the menstrual process there is a continual fluid and blood escape from the epithelial surface. The opening up of the adjacent regions of the stroma is probably to be looked upon as the result of the tendency of the fluid to escape into the regions of least resistance; it passes more readily towards the regions from which it is escaping.

In the present state of our knowledge it is impossible to state with certainty the manner in which the blood escapes into the uterine cavity during the bleeding stage of the menstrual cycle. We know that for four or five days previously the endometrium becomes swollen to two or three times its wonted thickness, due largely to a watery and hæmorrhagic escape from the distended vessels, and it would seem from the observations of some workers, *e.g.* Leopold, that with the onset of the menstrual flow the expanded mucosa sinks down to almost its ordinary size. These observations my specimens confirm. During the bleeding stage, except for an œdematous and a hæmorrhagic infiltration of the upper layers and a rugosity of the surface, there is little thickening of the mucosa (Fig. 6). These data, taken in conjunction

with the observations recorded in the preceding pages, would indicate that the conditions of the mucosa in the premenstrual and the menstrual phases are to be looked upon as representing two different stages in the same process. In the first the stroma changes culminate in an increasing dragging of the intravascular contents into the surrounding tissues, which become correspondingly expanded. In the second this process is combined with factors which force or transmit the fluid and blood across the tissue intervening between the vessels and the uterine cavity. What these factors are, whether an activity of a secretory nature on the part of the epithelial cells, or whether an activity on the part of the stroma, also secretory in nature, can only be a matter of theory. If the latter is operating, namely a secretory activity on the part of the stroma protoplasm (whatever this may mean in terms of chemico-physical laws), it seems to me that the active imbibition which has been noted in the preceding stage must be looked upon as representing the first phase of this process.

As has been seen by a study of the literature, there is some uncertainty regarding the exact mode in which the red cells reach the cavity of the uterus. The more recent researches would tend to indicate that there is little, if any, epithelial shedding during menstruation, and that the red cells escape, for the most part, across the unbroken epithelial lining of the surface and glands. This leaves only two methods of accounting for the leakage of the red cells; it must be through or between (Gebhard) the cells. In some of my specimens I have detected the presence of clear tracts in the epithelial surface, in some cases large enough to accommodate the red corpuscles, but I have never noted the red cells actually passing through in quantity.

Menstrual Œdema and Hæmorrhage in Extragenital Regions

We have seen that, according to the modern belief, menstruation is due to the action on the uterine tissues of a chemical secretion or hormone elaborated by the ovary and transmitted by the blood-stream. The limitation of the specific menstrual changes (hæmorrhage, etc.) to the mucosa indicates clearly the existence in this of a special adaptability to the effect of the circulating hormone. That there is, however, during this period an influence more widespread is a matter of common knowledge. This is evidenced in the general functional disturbances—malaise, etc.—present, and in such local signs as swelling and tenderness of the breasts, which precede and outlast the menstrual function. It is not unlikely that these signs and the uterine changes, which together

comprise the symptom-complex of menstruation, are dependent on the same ovarian secretion. It is especially interesting, in view of the changes which the endometrium exhibits, to find a synchronous swelling of the mammæ. This is usually described in the books as depending upon a congestion. It seems to me, however, not unlikely that the same process is operating here as was noted in the premenstrual mucosa, and that in these changes we have another index of the protoplasmic alterations which the circulating hormone can induce.

This hormone, I have shown from a study of the endometrial stroma, has the power of so changing the chemico-physical constitution of tissue as to lead to an active imbibition of the vessel contents. It is not surprising, therefore, to find that under certain abnormal states the circulating hormone should lead to irregular extragenital œdemas. Of such I have seen two well-marked cases. The first patient, who was a girl of nineteen, under the care of Dr. Haig Ferguson, had complained for several years of an œdematous swelling of the right hip and thigh, commencing and increasing gradually for a few days before the onset of her menstrual period, and disappearing after its cessation. This recurred regularly every month. The menstrual period was normal; the pelvic organs were perfectly healthy. The other case was somewhat similar in history; here the swelling involved the small of the back. These menstrual œdemas I would explain as due to changes provoked by the circulating hormone on tissues abnormally susceptible to its influence; the protoplasmic alterations lead to a fluid imbibition.

In some instances, as is well known, there may actually occur a hæmorrhagic escape from a mucous surface, usually that of the respiratory tract, at the time of the menstrual period. This vicarious menstruation is often associated with a suppression of the normal flow, and may recur with constant regularity once every month. Of this condition I have seen one undoubted case.

Summary

(1) The œdematous infiltration of the tissues which precedes the hæmorrhagic escape is due neither to a mechanical displacement or filtration of fluid from the vessels nor to a secretory activity of the intimal cells.

(2) It is dependent on protoplasmic changes which result in an *active* imbibition of fluid from the vessels. So far as we at present know, this change is due to a widespread liberation in the tissues of crystalloidal elements or of colloidal elements

with an increased affinity for fluid. The fluid diffuses from the vessels, teasing out the vessel walls and the surrounding stroma in the process.

(3) The stroma and vessels are especially adapted for such a process by virtue of the structural peculiarities previously noted. Additional evidence has been advanced in support of the belief that the intercellular spaces are completely walled in under ordinary circumstances. The so-called network corresponds to the fine films separating the fluid chambers of the functioning stroma protoplasm.

(4) The opening out of the stroma and vessels prepares the way for the escape of the corpuscles. This occurs by a process of diapedesis, and also as the result of a wholesale displacement of the vessel wall and stroma. Into the composition of the wall of the sinuses or lacunæ stroma cells largely enter.

(5) These vascular changes are probably chiefly due to the active fluid streams radiating from the vessels into the tissues. How far the ordinary *vis a tergo* dependent on the heart force acts it is impossible to say. It seems likely that it is insignificant.

(6) The endometrium, throughout its entire extent, must be looked upon as a potential blood sponge. It is so constructed as to permit, in response to the changes described above, an immediate flushing of any part with the blood fluid and corpuscles. The importance of this discovery in connection with pregnancy will be described in the succeeding chapters.

(7) The exact process by which the blood cells escape into the uterine cavity is still uncertain.

(8) The tissue changes are due to some material (secretion or hormone) liberated by the ovary, which reaches the protoplasm of the mucosa *via* the blood-vessels. (In subsequent chapters it will be shown that the biochemical substance derived from the chorionic cells produces changes in the maternal tissues in many respects identical with those described in the menstruating mucosa.)

CHAPTER III

MODE OF ACTION OF FŒTAL STRUCTURES ON THE MATERNAL TISSUES—TWOFOLD ACTION OF CHORION —PREGNANT TUBE

In the following pages I propose to discuss in detail the manner in which the maternal tissues react to the fœtal elements, the rationale of the changes in the uterine mucosa from the earliest discernible phenomena during pregnancy, and especially how the structural conformation of the stroma and vessels is adapted to the performance of these functional changes.

Intra- and Extra-Chorionic Activities of Fœtal Epithelium

The chorionic structures have two well-defined functions to perform in the fœtal economy. In the first place, through their action the fertilised ovum is enabled to obtain for itself a nest in the mucosa and to open up the maternal vessels, and in the second place, it is now recognised that by their means the ovum obtains the nutritional elements of the maternal blood lake in which it is immersed. Whilst the former of these activities is most evident in the earliest period of pregnancy, and disappears after a short period, the latter remains during the entire extent of intra-uterine life. The term *trophoblast*, first applied by Hubrecht to the thick layer of epithelium covering the early blastocyst, is convenient, but it must be remembered that the activity embraced by this word is twofold. It is more than a mere transmission of the nutritive elements from the mother's blood to the embryo. It includes also the changes in the maternal structures by which the blood-supply is obtained. The first faculty resides within the cells, and for it I would suggest the term *intrachorionic action of the trophoblast*. The second depends on extraneous changes induced by the chorion in the maternal tissues, and this we may conveniently express as the *extra-chorionic action of the trophoblast*. The advisability of clearly recognising the double rôle enacted by the chorion in its acquisition of food for the embryo will become apparent in the ensuing pages. The latter of the

above two faculties especially concerns us in this place, and with it I propose to deal in the first instance.

The mode of action of the chorionic structures can be studied satisfactorily only where the maternal changes are in full swing. In the uterine mucosa the manner in which the implantation chamber is formed, and in which the maternal vessels are opened up, is concealed after the very earliest stages. As I believe that the key with which to unlock many of the secrets is to be found only by a proper understanding of the exact details of the maternal reaction, I propose, by way of introduction to the study of the normally imbedded ovum, to describe the changes encountered in the wall of the pregnant tube, in chorionepithelioma, and in another condition in which an invasion of the fœtal elements is obviously present.

The order I propose to observe, then, in the description of the maternal changes is as follows:—

1. The Wall of the Pregnant Tube.
2. The Uterine Wall and other Tissues in Chorionepithelioma.
3. The Uterine Wall in a Simple Invasion by Retained Placental Fragments.
4. The Uterine Tissues in Normal Pregnancy.

THE PREGNANT TUBE

In tubal pregnancy the fertilised ovum becomes imbedded in the tubal wall. The site varies in different cases. It occurs most frequently in the ampullary or isthmal portion. More rarely the part of the tube which traverses the uterine wall — interstitial pregnancy — or the fimbriated end may be involved. The causes of this retention of the ovum in the tube are many. One cause of which there is little doubt is any obstacle to the free passage of the ovum along the tubal lumen. This may be of the nature of a fusion of the folds of the mucosa—the result of a preceding inflammation (Fig. 22)—or the ovum may have passed into and become stranded in a diverticulum of the mucosa into the muscular coat of the tube (Figs. 20, 23, 24). In other cases the ovum has passed into the *cul-de-sac* of an accessory ostium. Of this condition I have seen one case. Kinking of the tube, due to adhesions, or to a persistence of the fœtal convolutions, or a stenosis in the tubal lumen, may all obstruct the passage of the ovum, and thus lead to a tubal implantation. It would seem that in most cases the ovum develops at the immediate

site of the obstruction in the tube. As I have pointed out, however, it should be remembered that the ovum may become stranded external to a narrowing in the tubal lumen. The ovum bed may be separated from the obstructed region by a considerable interval. This is probably due to the fact that the ordinary stream of fluid along the tube, which wafts the ovum along, is slowed or stopped. The ovum is not even carried as far as the stenosed part.*

The pathological changes induced by the ovum differ greatly in different cases. By some means or other, the exact nature of which is not yet definitely settled, the ovum soon reaches the muscular wall of the tube. How this occurs is not difficult to understand in the case of a stranding in a diverticular protrusion of mucosa into the muscle. This, however, does not explain more than a small proportion of the cases. In the muscularis the ovum excavates its bed, in which it lies immersed in blood derived from the opened-up maternal vessels. In early cases it is often possible to recognise a layer of muscle and mucosa intervening between the ovum and the tubal lumen. This corresponds to the capsularis of uterine pregnancy (Fig. 20). Sooner or later, if the ovum continue its growth, the tubal wall gives way on the inner or the outer aspect. If this be sudden, it may lead to the immediate death of the fœtus; if the rupture be more gradual, and especially if it occur between the layers of the broad ligament, the fœtus may establish new attachments and continue its growth. It should be remembered that the expansion of the ovum cavity is not necessarily associated with a rupture as ordinarily understood, for in many cases it is found—and this description must apply to those instances where the fœtus reaches an advanced stage of pregnancy—that a giving way at any stage of the expansion is prevented by the adhesions which have previously been laid down. The irritation produced by the invading chorionic cells leads to a binding of the tube to the broad ligament, uterus, ovary, etc. By the time the affected portion of the tubal wall is destroyed the adhesions suffice to shut in the cavity. And so the process goes on—vascular adhesions to more and more distant structures being laid down as the chorionic elements insinuate themselves further and further into the maternal tissues. The same changes occur with a growth into the broad ligament.

Where the rupture occurs on the mucosa aspect the ovum may become aborted into the tubal lumen, and there it may lie imbedded in

* *Edin. Med. Journ.*, Aug. 1909, "Anatomy and Histology of the Pregnant Tube."

a mass of blood clot, somewhat like a hæmatosalpinx. In other cases it may become extruded from the abdominal ostium. Where the rupture is more or less sudden, and it occurs on the peritoneal aspect of the tube, there may be severe intra-abdominal hæmorrhage, and the ovum may be completely detached. Where the rupture occurs between the layers of the broad ligament a hæmatoma is produced.

Extrachorionic Activity of the Fœtal Epithelium in the Pregnant Tube

The material used for these investigations consists of ten specimens of tubal pregnancy. They were all removed by operation, and they were therefore obtained perfectly fresh. In the shortest possible time they were in each case placed in Pick's Solution (No. 1) for hardening. The desired portions of the tubal wall were removed and mounted in paraffin. They were then cut into serial sections, varying in number from 40 to 2000. Out of the total number of specimens examined I propose to limit my description of the histological details to six of them, in which the fact that the embryonic structures are in a perfect state of preservation indicates that the changes present in the tube are not dependent on the process of degeneration or repair subsequent to the death of the chorionic cells. The approximate durations of the pregnancies vary between fourteen to sixteen days and four months.

In the wall of the pregnant tube it is found that where the chorionic cells come into contact with the maternal structures there is present a zone of markedly degenerated tissue; the cell outlines are obscured or have disappeared, the nuclei have disintegrated, and there is produced a homogeneous necrotic surface which forms the confines of the ovum bed. One of the most characteristic features of this necrotic zone is the extensive infiltration of the tissues with red blood corpuscles (Plate V.). There is usually present, also, a marked œdematous exudate.

Imbedded in this degenerated tissue, which is formed chiefly of disintegrated muscle, there are often seen cells which contain a pale nucleus and attain a very large size. The main feature of these cells is the enormous increase in the cell body, a trait which identifies them with the decidual cells in the uterine mucosa which are found in normal and also in tubal pregnancy, and which are produced by an enlargement of the stroma connective-tissue elements. It seems certain that in the tube, also, these cells are connective tissue in origin. The structure of the tubal wall, in which the connective tissue elements

are not massed together as in the uterine mucosa, precludes the possibility of a decidual formation occurring to the extent present in the uterus. In the tube the change is, for the most part, indicated only by the presence of these transformed cells scattered irregularly about the muscular tissues. An exception, however, must be made to this general statement in view of the fact that the connective tissue of the mucous ridges of the tube, which corresponds closely to the stroma of the uterine mucosa, is able to undergo a change identical in many respects with that found in the decidual membrane of ordinary pregnancy (Plate IX. and Fig. 32).

Whilst the above-mentioned vascular and tissue changes are detected in the most marked degree in the immediate vicinity of the ovum, they are by no means limited to this region. By most observers they are recognised as due to some biochemical substance liberated by the cells of the developing chorion. The probable nature and properties of this fœtal influence I shall discuss in greater fulness in a subsequent section; in the meantime I shall follow the usual practice and refer to it under the rather vague terms of "chorionic influence," "fœtal activity," etc.

As far as is revealed by a study of the *literature* on tubal pregnancy, the expression of opinion is unanimous in favour of the belief that the developing chorionic cells procure their requisite blood supply by destroying the maternal vessels which they encounter in their advance. As to the exact nature of the destructive activity with which the chorionic epithelium is endowed, there is some divergence of opinion, and not a little ambiguity, in the literature. Some authors, such as Heinsius, Webster, Fellner, Raschkes, Schambacher, Berkeley and Bonney, Whitridge Williams and others would seem to incline to the view that the opening up of the vessels is due to an active cellular invasion of the maternal tissues by the chorionic off-shoots—these, after becoming engrafted on to the tubal wall, destroy and replace the maternal structures, and in this way create gaps in the vessel walls. Other observers, such as Kroemer and others, endeavour to explain the phenomena not by actual cellular incursions of this nature but rather by a sort of softening and corrosion of the tissues. When the process involves the wall of the vessel this gives way, permitting an escape of blood round the advancing fœtal structures.

For the purpose of testing the validity of these views, and, if possible of arriving at some definite conclusion on the subject, I have carried out an extended investigation in my specimens. To obviate as far as possible the risk of an erroneous interpretation of the appearances

presented, the examination has been conducted exclusively by means of serial sections.

As regards the first of the above-mentioned views, namely that the opening of the vessels is dependent on a projection of the chorionic buds into the maternal structures which become destroyed and replaced, the evidence derived from an examination of the specimens is at first sight somewhat ambiguous. The specimens exhibit the well-known appearance in the fact that round the periphery of the ovum bed the fœtal cells have here and there become engrafted on to the wall of the tube. Where this has occurred the portion of the tube wall appears to be eaten away and replaced by chorionic cells which are incorporated with the maternal tissues or are unattached and lie free in bays formed in the surface of the tubal wall, forming the confines of the ovum bed (Figs. 25, 26). Where the fœtal ectoderm has encountered a vessel in its progress the same process has taken place, till in some cases the embryonic cells are seen to have bored right through the vessel and project into the lumen (Fig. 27). This action is certainly usually not difficult to discover, though in my specimens it is not present to any considerable extent. The true interpretation of this appearance I shall describe in a later section. In the meantime I would suggest, as a logical conclusion, that *per se* an invasion of the wall of a vessel by the chorionic cells would not be likely to lead to a wholesale gaping without some other process, *e.g.* softening. It seems likely that the replacement of the destroyed tissue by the fœtal cells would plug the breach produced, and would thus prevent the mechanical escape of the blood.

Whilst the process just described culminates in the part of the villus which is free in the vessel lumen becoming bathed in blood, it does not account for the wholesale gaping of the maternal vessels round the wall of the fœtal cavity, which pour their blood into the intervillous reservoir. In some regions, it must be admitted, it is possible to detect the spread of the chorionic cells for some distance along the inner aspect of the wall of a vessel which has become opened out into the intervillous space. In my specimens this was detected in only a few places, and is amply accounted for by the fact that it happened to be the spot at which the chorionic cells had alighted. That the free ends of the villi floating in the intervillous space may be carried into the open mouths of the vessels has been repeatedly described by previous observers. After gaining an entrance the villus may grow for a considerable distance along the vessel. This process, which has been termed by Veit "deportation of the villi," occurs both in tubal and

in uterine pregnancy (Fig. 35). Detachment and carrying away of fœtal cells from these intravascular villi has been advanced by the same author to explain the etiology of eclampsia. The entrance of these villi into the vessels might at first sight suggest that the apertures produced in the vessel wall had been due to a direct spread of the fœtal villi through the wall, and that their further growth had given rise to the appearances noted above. This argument, however, is undermined by the demonstration of Veit that the villous growth has occurred only along the veins, and he therefore suggests that their situation within the vessel lumen is to be explained by the fact that they were carried there by the force of the blood-stream subsequent to the opening up of the veins. With the truth of this observation I agree.

That a direct cellular invasion of the fœtal villi is discredited as a satisfactory explanation of the phenomena is proved, in addition, by the fact that in many places the mouths of the vessels which discharge their blood into the embryonic space are found to be situated at a distance, sometimes considerable, from the sites where the fœtal cells are engrafted on the tube wall. As a matter of fact, in my specimens *this engrafting has occurred only to a comparatively small extent, and certainly in a degree much smaller in proportion than the number of the opened-up vessels.* The only logical conclusion from these observations is that the vascular gaping is produced by some influence other than the process conjectured by the aforesaid authors. It would seem to be in the light of these facts that some authors have endeavoured rather to attribute the destruction of the vessel walls to the softening or corroding action of some material liberated by the chorionic cells, and this explanation would certainly meet the case more satisfactorily. It would seem not improbable that, in advance of the developing villi, the structures of the tube wall are by this means softened and dissolved, and, the vessel walls sharing in the process, that the blood circulating in their channels is liberated and discharged through the gaps thus created into the inter-villous space. This view affords an ample explanation of the above-mentioned facts, that the vessels opened up are often situated in regions at a distance from the infiltration of the chorionic cells. This interpretation of the phenomena also possesses the advantage of explaining the fact, which, though remarkable, has received only a scanty attention in the literature, namely, that the dimensions of the ovum cavity in the tube, as in the uterus, are greatly in excess of the requirements of the ovum and its villous projections. This provision, of course, is necessary for the existence of a blood-filled

intervillous space, and is in all probability attained in part by a dissolving influence such as we have described.

We thus see that whilst the facts are completely at variance with the views entertained by the first class of observers mentioned in a previous paragraph, they conform at first sight with the opinions advanced by the second class. Do these, however, constitute a full and efficient explanation of all the phenomena? My researches have led me to answer this question in the negative. My specimens have furnished evidence which, in many respects, is fundamentally opposed to this simple explanation.

If we examine the tube wall behind that part forming the limiting surface of the ovum cavity, we find that the vessels exhibit remarkable changes, changes which must be considered as casting important light on the manner in which the vessel lumina in immediate proximity to the ovum are brought into direct continuity with the intervillous space. These changes are most evident in the region of the tube forming the wall of the gestation cavity, and become less and less marked as this is left. They are, however, still detectable at a considerable distance from the site of the ovum.

In the degenerating tissue, which bounds the intervillous space, blood-vessels, whose walls exhibit varying stages of disintegration, are seen. Sometimes they are small, in other cases they are dilated. In some instances the distension of the lumen reaches an enormous degree. The maternal tissue septum between the blood-vessel lumen and the intervillous space may be extremely thin. This is due, in many cases, largely to an actual advance of the blood cavity of the vessel towards the intervillous space. From the vessels it is often possible to see a passage of red cells into the adjoining necrosed tissues, and certainly in regions where there are no chorionic cells. In many places there may be a wholesale leakage of red corpuscles across the space intervening between the vessels and the intervillous space. The great distension exhibited by some of the vessels and the exodus of the red corpuscles into the intervillous space even before there is an actual breach in the intervening septum would tend to suggest that there must be some influence at work conspiring to soften and tease apart the vessel boundaries, an action which leads, in the case of those vessels in immediate proximity to the gradually receding surface of the ovum cavity, to an increasing thinning out of the wall, which ultimately gives way, permitting the affected vessel to contribute its share to the intervillous reservoir.

If we can arrive at some definite conclusion as to how this process occurs we shall be furnished with important information regarding the mode of action of the chorionic ectoderm in the tubal wall. In the first place, in the description just given, which represents the typical condition in these parts of my specimens in which we can follow the process in all the stages short of an actual wholesale breach in the vessel walls, it will be freely admitted that the opening up of the vessel cannot be dependent on a direct invasion by the chorionic cells. It is obvious, in addition, that it is not due to a softening and destruction of the tube wall, which advances gradually from the bounding surface of the gestation sac outwards, opening up the vessels encountered *en route*. It may, at first sight, seem possible to explain it as due to a gradual expansion of, and blood escape from, a vessel due to the soft and distensible nature of the medium in which it courses, and to an ultimate giving way when the tissue between the two bloods is reduced in thickness to such an extent as to be unable to resist the intravascular blood pressure. This simple interpretation, however, does not solve the problem.

The portion of the tube wall bordering on the ovum cavity is extensively infiltrated with red blood corpuscles. These are especially numerous round the vessels. This condition is, however, present, sometimes to a marked degree, even at a considerable distance from the ovum. In Plate V. is shown a section demonstrating these appearances in a lucid manner. In the lower part is seen the intervillous space, in which several villi are pictured. The immediately adjacent tube wall is undergoing a marked fibrinous degeneration, and is interspersed with extravasated blood. Above this a less necrosed portion of the tubal wall is shown. Here and there, especially round the blood-vessels, there is likewise a hæmorrhagic extravasation. The red cells are streaming out through the wall into the surrounding tissue, which has been opened out by a previous œdematous exudate. With the red cells there are also present considerable numbers of leucocytes of all types, the polymorphonuclear predominating. The tissues in which the changes are taking place are softened and degenerating.

With regard to the distension of the vessels there is a point of considerable interest and importance. The increase in the diameter of the vessel lumina often does not occur in a regular and uniform manner such as we associate in other parts of the body with an enlargement due merely to an increased intravascular tension. The distension in this case is of an uneven, sometimes very irregular, nature. The walls open out more at one part than another, the result being

the transformation of the ordinary rounded contour into one ragged and uneven. In a short time the confining wall becomes completely teased asunder, and the blood comes to be contained in an uneven space formed entirely by the opened-out surrounding tissues. The appearances presented by the expanded blood spaces in the necrotic tissue suggest that the expansion takes place at the expense of a softening and solution of the boundary wall and the adjacent tissues, a change which steadily progresses till the originally comparatively small vessel is transformed into a large and still increasing blood space or cavity. Even then, round the margins of this there is often seen on sections to be a free exodus of the contained corpuscles into the adjacent tissues. This condition is present round the entire circumference of the ovum cavity.

In the proximity of the ovum the histological changes in the tissues are obscured because of the degree to which they have succumbed to the fibrinous degeneration, and, to obtain information of an accurate nature regarding the actual changes present, we have to carry our attention to the vascular alterations in the tube wall at a greater distance from the ovum. The evidence thus acquired will enable us more readily to understand the changes to which I have referred. As we pass further and further from the gestation cavity we find a gradual diminution in the grossness of the vascular changes. The crumbling away of the walls, with a wholesale extravasation of the contained blood into the surrounding tissues, which we encounter in the immediate proximity of the developing ovum, becomes gradually less and less evident, and is replaced by a softening and expansion of the vessels, with here and there small areas of blood escape into the vessel wall and the adjoining tubal tissues. Throughout the entire extent of the affected tube there are found large irregularly-shaped, sinus-like blood spaces, with a distinct endothelial lining, resembling, in every respect, the blood sinuses which develop in the endometrium and in the muscular wall of the uterus during ordinary pregnancy. In some cases they are found in the near vicinity of the intervillous space. The mode of formation of these blood tracks in the tubal wall and its possible bearing on the manner of origin of the similar uterine lacunæ will be described in a subsequent section of this research.

Explanation of Opening up of Vessels—Cause of Œdema

In endeavouring to determine the manner in which thc teasing out and gaping of the vascular wall oecur during tubal pregnaney our purpose will be best aecomplished by directing our attention, in the first plaee, to the ehanges exhibited by the vessels at a eonsiderable distanee from the ovum, in regions where the condition is definitely established. Passing thenee by degrees to the region of the gestation eavity, we are enabled to traee the proeess from a mere softening to the wholesalc destruction of the vessel walls in the immediate vieinity of the embryo.

In Fig. 28 is shown a seetion of a small vessel, the wall of whieh is represented by a homogeneous, fibrinous material, in which there are present a number of well-preserved nuelei. Pervading the wall a number of clear spaces are seen, which on seetion are represented by vacuoles. These, though present throughout the entire thiekness of the wall, are most evident immediately under the endothelial layer. The changes which are present here, and whieh, as will be subsequently shown, are found widely scattered throughout the tubes, might at first suggest the existence of a fatty degeneration of the tissues, the elear spaces eorresponding to fat globules which have been dissolved in the preparation of the seetion. That this is not so is easily proved by preparing the fresh specimen and then staining it for fat. I mention this point here to dispose of it onee and for all. The resemblanee to a fatty degeneration whieh appears at first sight will be found to completely vanish with a fuller study of the changes.

The adjoining tissues of thc tubal wall are spread apart by an œdematous exudate. The œdematous infiltration of the vessel wall and surrounding structures represents a condition which, as we have already mentioned, is widely spread throughout the pregnant tube. It is usually most evidcnt in the immediate environment of the vessel, and it is due to some influence leading to an increased escape of fluid from vessel lumen to tissue spaees. The well-supported vascular walls are for the most part not involved in the process to the same degrec as the more displaeeable structures of the tubc, but that they share sooner or later in the change is shown by the figure.

The structural changes underlying this dropsieal infiltration of the vessels, which play an important *rôle* in thc softening and ultimate giving way of thcir walls, are, in all probability, closely allied to those which operate in the production of œdema in general. Oceurring, as it does

in the condition which we are investigating, in the wall of a markedly degenerating tube, it is possible that factors may be introduced which differ in kind or degree from those concerned in the production of œdema in other regions. The different conceptions entertained with regard to the cause of a fluid escape from the vessels have been referred to in the last chapter, and they will be discussed in the Appendix. It is obvious that any disturbance of the different conditions, normally acting in harmony, may determine the production of a dropsical state. This disturbance may be of the nature of an increase in the blood-pressure or a change in the composition of the blood; it may depend on a pathological state of the endothelium or an abnormal composition of the tissue elements, resulting in the production of diffusion, osmotic, or other currents. That a mere lymphatic obstruction fails to account for the œdematous changes is proved by finding distinct evidence of an increased escape from vessels to tissues.

As already indicated, a study of my specimens has convinced me that the changes operating in the softening and opening up of the vessels in the tubal wall during pregnancy in that region are intimately bound up with the structural alterations which lead to an œdematous infiltration of the vessel walls and tubal tissues. This is associated with a teasing asunder of the elements which constitute the walls of the vessels, and is followed sooner or later by a breach in continuity with the production of a track or tracks leading directly from vessel lumen to tissue or intervillous space. It is obvious, therefore, that any investigations which cast light on the mode of production of this dropsical escape must carry us a long way towards a proper understanding of the manner in which the ovum engrafted in the tube wall is furnished with its blood supply.

In conducting this inquiry I have followed the lines indicated by previous workers on the production of œdema, in so far as this includes a scrutiny in succession of the possible determining agents. My investigations, however, have necessarily differed from theirs in the fact that I have carried out my research by the aid of the microscope and not by means of experimental measures. So far as I know, the observations recorded in this chapter and in Chapter I. incorporate the first attempt ever made to elucidate the problem of œdema-production by means of a histological survey of the tissue elements concerned in the process. This fact would indicate that any light cast on the subject by this means will, in addition to affording us assistance in our local

inquiry, add evidence of a different nature from that hitherto obtained in regard to the study of œdema in its more general aspects.

In approaching the study of the changes responsible for the œdematous ploughing up of the vessel walls and tube tissues to which we have already referred, it will be well to consider them under the following headings, namely (1) alterations in the blood; (2) changes in the fine membrane formed by the endothelial layer; and (3) changes in the rest of the vessel wall and the surrounding tissues.

As regards the blood contained in the vessels, changes may occur in two different directions, in the form of altered composition or altered pressure. *An alteration in the constituent elements of the blood* cannot *per se* lead to an increased escape of fluid through the vessel walls. Any interchange of fluid between blood and tissue, in the form of an increased transference from vessel, must be dependent on an alteration in endothelium or tissue except in the case of a mechanical filtration, which comes into consideration under the heading of altered pressure. In this place, however, it is necessary to state that the biochemical material emanating from the chorionic cells, and which would seem to be the primary causal agent in the changes under discussion, may possibly be carried to the affected regions by means of the blood-stream. This reservation, which does in no way affect our present argument, will be more carefully discussed in a subsequent part of this book.

Is the dropsical exudation, then, to be explained by a *mechanical escape* of fluid from vessel lumen into vessel wall and thence to the tissues? This explanation would at first sight seem to accord with the established facts, namely that, in the first place, during pregnancy there is a well-marked local congestion and probably increase of intravascular pressure, and that, in the second place, there is a degenerative softening of the tissues. These two conditions, acting in consort, might be supposed to explain the facts adequately, the first resulting in an increased transudation of fluid across the vessel walls, the second allowing of an easy detachment and displacement of the elements of the vessel wall and tissues. That the phenomena, however, are not amenable to such an easy interpretation is proved by a study of the histological changes present.

The ploughing up of the vessel walls by the watery escape may, for purposes of description, be divided into three stages marked off from one another more or less roughly. In the earliest stage the

condition has involved the inner portion of the wall, which is seen to be beset with a number of fluid tracks, which on section appear as clear vacuoles. In the next stage the condition has involved the entire thickness of the vessel wall, whilst in the last stage there is a wholesale ploughing-up of the wall with the creation of gaps, which establish a direct communication between vessel lumen and tissue spaces. Throughout the process the surrounding tissues of the tubal wall are the seat of a watery infiltration, whose intensity in many places is seen to vary in proportion to the degree of damage of the vessel wall. In some cases it is easy to detect varying degrees of these changes in different parts of the same vessel. In Fig. 28 is shown an example of the first stage, in Fig. 29 one of the second stage, whilst in Fig. 30 is shown an example of the third stage. Here, besides a wholesale escape of fluid, which is readily recognised in the other cases, there is occurring hæmorrhage into the neighbouring tissues.

That a mechanical infiltration into, and displacement of, softened tissues does not suffice as an explanation of the phenomena is revealed by a more careful study of the changes. In Figs. 28, 29, and Plate VI. it is seen that *the fluid which has passed into the vessel wall and has accumulated in spaces toward its inner aspect has led to a lifting up or projection of the endothelial cells into the vessel lumen in the form of distinct bulgings.* In some cases this condition is associated with knoblike swellings formed of the individual cells; in other cases it is represented by a separation and bulging towards the lumen of the endothelial layer of cells, which have become detached as a sheet. These appearances, which I have been able to detect with ease in all my specimens of tubal pregnancy, demonstrate that in the transference of the fluid from the vessel lumen, which has accumulated in the inner part of the wall and led to a displacement of the endothelium, there has been in operation a force other than a mere mechanical filtration across a membrane from a region of higher to one of lower fluid pressure. In fact it is obvious that, so far from this being the explanation of the phenomena, *the fluid leading to the endothelial uplifting must actually be under a hydrostatic pressure higher than that in the vessel lumen.* The extent to which this change occurs in different vessels and in different specimens varies within wide limits. As a general rule it may be laid down that the better supported the vessel wall and the greater the success with which it resists the softening and exudative process, the more marked the involvement of the inner part of the vessel wall.

This fact is not difficult to explain. The greater the implication of the outermost parts of the vessel wall in the process, the more readily can the fluid which is being abstracted from the vessel be passed on, relieving in this way the fluid tension on the endothelial aspect. (Compare with the description given in Chapter II. of the vessel changes in menstruation.) *These appearances, which are present in my fresh sections, demonstrate, moreover, that the force determining the fluid exchange must be considerably in excess of that of the pressure of the blood* in the vessels.

A more careful examination of the exact histological changes associated with this dropsical condition of the innermost part of the vessel walls reveals some facts of considerable interest and importance. In some cases the œdematous exudate has collected *under* the endothelial cells. This is invariably the condition present when the fluid accumulation has occurred to any marked extent. When there is a wholesale detachment of the endothelial layer it is obvious that the fluid must be contained, for the most part, in a space entirely sub-endothelial in position. In other cases, however, the watery escape is associated with a fluid accumulation *in* the endothelial cells. This hydropic distension of the individual cells, which in pathological text-books is somewhat erroneously termed "vacuolation," is accompanied with a marked swelling of the cell, the cell substance being displaced by the accumulating fluid to the periphery, where it is represented often merely by a fine film. The detection of this film of cell protoplasm is sufficient to indicate that the fluid accumulation has occurred within, and not outside, the cell. The distending fluid has likewise led to a displacement of the nucleus to the surface of the cell, and the result produced by the clear space, surrounded by the pellicle of cell substance, with the nucleus at the pole, has been designated by the term of the "signet ring" appearance. The changes in the nucleus are usually characteristic; it becomes flattened and drawn out, often occupying a large area of the circumference of the cell, and it is interesting to note that in the larger number of instances it is displaced towards the part of the cell projecting into the cell lumen. These appearances I have already referred to in the menstruating mucous membrane of the uterus. In that region they were seen, as here, to be associated with an escape of fluid from the vessel lumen into the tissue spaces.

This hydropic distension of the cells is sooner or later followed by an escape of the contained fluid into the region immediately underlying. This would seem to be preceded in most cases by a disappearance or

rupture of the intervening sheet of cell substance. It would seem not unlikely that, after the distension has occurred to a certain extent, the intracellular tension created will suffice to lead to a giving way of the fine film, with an escape of the fluid. In some cases it is possible to recognise what appear to be the severed edges of this sheet. How far the distension of the cell can take place without a separation of the cell boundary it is difficult to say. In some specimens this would, at first sight, appear to be very great indeed (Plate VI.). In these cases, however, it is more likely that what apparently looks like the boundary of a largely distended cell is, in reality, formed of the rounded wall of a space formed in the surrounding tissue. It is often seen that the fine partitions intervening between the contiguous, distended endothelial cells disappear, and in this way a track filled with fluid of varying lengths may be formed. With the teasing out of the adjacent part of the vessel wall there is apt to be an obscuring of the true nature of the process at work.

In the *second stage* of the arbitrary division, which we made for the purpose of facilitating the description of the process, the condition which we have seen present in the innermost region of the vessel wall has spread to the extent of involving its entire thickness. Here the œdematous infiltration of the vessel is represented by the presence of a large number of fluid tracks, which on section often again look like vacuoles occupied by clear fluid. These spaces can often be recognised to be in direct continuity with those under the endothelial layer, and they can likewise often be traced directly into the perivascular tissues of the tube wall. In Fig. 29, in which such a fluid track has been exposed throughout its entire length in the section, the wall is seen to be channelled from the region of the sub-endothelial space right into the surrounding part of the tube wall, the tissues of which are ploughed up by a watery exudate. In all the specimens belonging to this stage there is still, however, no complete breach in continuity in the course of the vessel wall, and whilst the change is associated with an increased fluid escape into the neighbouring tissues, the teasing apart of the wall has as yet not taken place to the extent of permitting an escape of the corpuscular elements of the blood. The extent to which this œdematous softening of the vessel wall can occur, short of the occurrence of a complete breach, varies within wide limits in different vessels of the same thickness. In some cases it is indicated by a number of small vacuolated spaces scattered irregularly throughout the wall. In other specimens, on the other hand, the vessel wall is pervaded, and

in some instances almost completely replaced, by spaces, which by their confluence have led to the production of fluid cavities of large size. As a general rule it may be stated that in vessels of the same thickness these structural changes are more evident the nearer the vessels are situated to the developing ovum.

We have already seen that in the fluid infiltration of the innermost portion of the vessel wall we are compelled to invoke some explanation other than a mere mechanical separation of the elements forming the wall, or a transudation from a region of higher to one of lower fluid pressure. This conclusion was suggested and substantiated by the changes which are induced by the process in the structure and position of the endothelial cells. From the detailed description just recorded of the changes as they advance outward to involve the other parts of the vessel it would seem that sufficient has been said to warrant the conclusion that here again the same process has been in operation. That the separation and spreading apart of the structures forming the degenerated vessel wall is not due to a merely mechanical influence is strongly indicated by the fact that the results, as evidenced by the histological findings, coincide in every respect with those already noted in connection with the endothelial and immediately sub-endothelial part of the vessel. If further proof of this contention were necessary, it is derived from the fact that here again the fluid contained in the tracks channelling the vessel wall must be under a tension actually higher than that in existence in the vessel lumen. This is demonstrated by the fact that these fluid spaces or channels are seen to be in direct continuity with similar spaces, in which the fluid has collected under, and led to an inward projection of, the endothelial cells (Plate VI.). A demonstration, moreover, of the fact which is furnished by a number of my specimens, namely that the tracks of the œdematous escape, where it leads to a ploughing up of the surrounding tissues, is in direct structural continuity with such endothelial spaces, would indicate that in the transference of the fluid from the vessel lumen to the tissues there must be in operation some force of a potent nature. We have already excluded changes in the composition or the pressure of the blood as the causal agent, and we are thus reduced, in our quest after the secret, to some alterations in the tissue activity of the structures of the vessel wall or the surrounding part of the tube.

In some of the vessels still situated at a distance from the actual site of the cellular invasion of the tubal wall by the fœtal trophoblast, the process described in the foregoing pages has advanced to the extent of

resulting in a wholesale crumbling and solution of the vessel wall and the creation of gaps leading to the establishment of an uninterrupted communication between the vessel lumen and the surrounding tissue spaces. In such cases there is present a wholesale extravasation of blood corpuscles into the perivascular tissues (Plate V.). It is noticeable that this blood escape from the thick-walled vessels has occurred to any considerable degree only in the proximity of those vessels where the fluid infiltration has led to the production of a breach in the vascular wall. There is often detected, however, a certain amount of blood escape into the vessel wall and the surrounding tissues, even in the case of those vessels where the teasing asunder has not taken place to this excessive degree. Red cells, singly or in small numbers, are often seen lying immediately under a detached endothelium or in the clear tracks which canalise the vessel wall, the endothelium of which is, in some cases, perfectly retained. It sometimes looks as if the red cells have actually passed into the interior of a vacuolated endothelial cell. These appearances suggest strongly that there may be a certain amount of blood escape from the vessel lumen even in the absence of a demonstrable track leading from the interior of the vessel. It would seem obvious that the escape of the more solid constituents of the blood necessitates a certain degree, however small, of separation of the cellular elements of the vessel lining. It is possible, where these are not detectable by the microscope, either that the spaces left are too small to be recognised, or that they have closed in again after the passage of the corpuscles in a manner something similar to that which is supposed to occur during the process of phagocytosis.

In the case of the thicker-walled vessels, how is the complete communication between the lumen and the surrounding tissue finally established? We have been able to follow with a considerable degree of precision the manner in which the sub-endothelial region is brought into communication with the outer tissue spaces. The completion of the process is a little more difficult to understand. In some cases, even at an early stage of the hydropic infiltration of the vessel wall, the endothelial cells are detached from one another, or they are seen to be lifted up completely from the underlying tissues. In such vessels the continuation of the process, in the way in which we have described it, will eventually result in the complete detachment of the endothelium, and the production of a complete gap in the vessel boundary. In some vessels, however, the endothelium may be retained even at a late stage of the process (Fig. 29). How, in such a case, does the parti-

tion still remaining between vessel lumen and tissue, in the form of the endothelial lining, become disposed of? It is obvious that an increase in the tension of the escaping fluid would suffice to completely detach the endothelial cells. Or the degenerative processes which have preceded, or are progressing *pari passu* with, the other changes in the vessel wall may determine a softening and disappearance of the endothelial remnants.

That even the comparatively small additional force necessary to displace the fine lamella of vessel wall still persisting is not derived from the intravascular tension is suggested by the fact that, in a part of the vessel wall, which lies immediately adjacent to a region of complete separation, there may still be present an inward projection of the fine endothelial layer. However accomplished, the establishment of a complete and uninterrupted connection between lumen and tissue, permitting of a wholesale escape of all the constituents of the blood would seem to be an inevitable consequence of a steadily increasing involvement of the vessel wall by the process of displacement and solution which we have described.

In all my specimens of tubal pregnancy, in which the chorionic cells were found to be well preserved at the time of examination, the changes above recorded were detected in the vessels. The degree in which the tubal wall is involved in the process would seem to be for the most part proportional to the size of the engrafted ovum. The distance along the tube to which the structural alterations have extended is smallest in the youngest specimen of the series, and is greatest in the oldest specimen. In one of the older specimens, in which the pregnancy has occurred in the ampullary part of the tube, the softening and dropsical infiltration and detachment of the vessel walls is present to a marked degree even in the thick-walled vessels towards the inner end of the tube (Fig. 33).

The description of the vascular changes hitherto recorded has more especially dealt with the thicker-walled vessels, in which the more rigid walls have resisted the process to a greater degree than the thin yielding walls of the smaller vessels. This resistance to the influence conspiring to detach the structures of the vessel wall has, in the case of the thicker vessel, forced, as it were, the process into prominence, and has presented to us evidence of a more legible nature in our attempt to decipher the secret underlying the manner in which the growing ovum is furnished with the supply of maternal blood (*cf.* menstruation). In regard to the smaller vessels we shall have to study, and endeavour to

explain, some rather remarkable changes which they exhibit. In the meantime it may be stated that in the case of these the fluid exudation and blood extravasation have occurred in the same way, and are, on the whole, more evident than in the thicker-walled vessels at the same distance from the ovum.

It is by the process described that the gross vascular changes in the proximity of the ovum are produced, changes which I referred to at the commencement of this discussion. The softening and separation of the wall with the subsequent increase in the diameter of the vessels in this region would seem to be entirely dependent on changes of this nature. The fact that the process can be traced with accuracy through all the stages, from the dropsical infiltration of the innermost part of the vessel wall up to a complete severance of the constituent elements by the same means, would seem to prove beyond doubt that the gross structural alterations detected in the neighbourhood of the chorionic cells must be attributed to some influence other than a mere mechanical giving way of softened boundaries before an enhanced blood-pressure. The changes present are much more complex, and are associated rather with some structural alterations, which enable the tissues of the vessel wall or the surrounding area to pass on or imbibe the fluid from the blood. The tissues, in other words, assume an active part in the fluid escape, and are not merely in the condition of a medium exhibiting a passive outward displacement. A recognition of this fact alone suffices to explain the conditions encountered. Dependent, as they must be, on some influence emanating from the growing ovum, the vascular changes are most evident in the proximity of the fœtal elements, where this influence of whatever a nature it may be, is most felt. As this fœtal stimulus gradually extends the sphere of its activity, more and more distant regions of the tubal wall come successively under its sway, the changes gradually diminishing in intensity as the region of the ovum is left behind, until ultimately they completely fade away. These facts would suggest that the chorionic influence may be of a chemical nature, perhaps of the order of an enzyme. This point will be discussed more in detail in a subsequent section of this research.

In this place it must be recalled that the exact nature of the process by which the wholesale gaping of the vessels on the surface of the gestation chamber occurs is, in this region, obscured often to an extent which renders it unrecognisable. This is due to the excessive degree to which the degenerative processes have advanced. In this location the vessel walls and the surrounding tissue are often repre-

sented by a structureless, fibrinous material, richly sprinkled with blood corpuscles. It is interesting, however, to note that traces of the process can be detected even here. The degree of opening up of the vessels bordering on the intervillous space varies from an extensive gaping of the wall to a condition in which there is still left a considerable interval of the degenerating tube between the blood lumen and the intervillous space. Even in the latter case there is seen to be a wholesale exodus of the contained blood into the surrounding tissues, with a coincident teasing asunder of the vessel boundaries. The consequence of this is that *the vessel invades the neighbouring territory and advances to join the large blood track.* It is interesting to note that even in the degenerated region of the tube wall there are still present numbers of well-preserved nuclei, which, in all probability, correspond to connective-tissue cells, which resist the degenerative influence to a remarkable degree. In the changes which these cells exhibit there is evidence that they are acting in such a manner as to lead to an imbibition of fluid from the neighbouring blood tracks. This fact will be described in greater detail in a subsequent paragraph.

The process underlying the teasing out of the walls of the maternal vessels, by means of which the growing ovum secures its supply of blood, we have seen is not amenable to a purely mechanical interpretation; it is dependent on a change of greater complexity than a mere giving way of softening walls with a squeezing out of the contained blood fluid and corpuscles. We have likewise adduced evidence to prove the invalidity of the orthodox belief that the necessary blood supply is procured by a destruction and displacement of the vessel walls by the locally invading chorionic cells. If these explanations fail to elucidate the factors in operation, what other process must be invoked? Reference to the list of the possible agents responsible for an increased escape of fluid from vessel to tissue reveals the fact that, having disposed of the blood, our inquiry is now limited, in the first place, to the endothelium, and, in the next place, to all the structures situated external to this.

Significance of the Endothelial Changes

Can a selective or secretory action of the endothelium be entertained as, of itself, an adequate explanation of the changes induced? The structural changes in the endothelial cells might, at first sight, appear to afford an affirmative answer to this question. The process, in its incipient stages, is often associated with a fluid imbibition leading to a distension or vacuolation of the individual lining cells. This change is to be

considered, without doubt, as a precursor of the more marked subsequent fluid transference. Is it to be regarded as bearing a causal or merely an incidental relationship? That the endothelial vacuolation, which is, almost doubtless, associated with the process underlying the œdematous escape, is probably to be looked upon as a degenerating change would seem to be indicated by the ensuing cell changes which are detected. After a certain degree of distension is attained there occurs a separation of the cell wall, with a consequent amalgamation of the cell cavity with that of its neighbour or the fluid space under the endothelium. We have already seen that this disappearance or rupture of the adjacent cell membranes may result in the production of a fluid track continued for a considerable distance along the vessel and representing the running together of the vacuolated cells. In other words, the changes described correspond in every detail with those found in the so-called hydropic degeneration of tissues. The fluid contained in the spaces thus created towards the endothelial aspect of the vessel is under a tension higher than that existing in the vessel interior. If it be maintained that these changes do not *per se* contra-indicate the existence of a specific secretory faculty on the part of the endothelial cells, it must, I think, be freely admitted that the force exercised by the escaping fluid, which such an action might transfer from vessel to tissue, must be inadequate to determine the drastic changes present. It is inconceivable that the tension of the fluid which the cells might secrete would be alone sufficiently great to lead to the wholesale detachment and teasing out of the structures which occur even in a thick-walled vessel, and at the same time plough up the adjoining tissues.

That the œdematous softening of the vessel walls is not due to an increased endothelial activity is proved, in addition, by the fact that the changes are present even in the cases where the endothelium has been detached. But, it may be urged, is it not possible that in these vessels the œdematous infiltration which has been inaugurated by the activity of the endothelium may, subsequent to its removal, be carried on by a mechanical opening out of the wall by the liberated blood? It may be asserted that now we have lost the clue, in the shape of the projection of the endothelium into the vessel lumen, which could be explained only by assuming the existence of some cellular or tissue activity causing the fluid escape. This objection, which at first sight seems difficult to meet, is easily disposed of by the fact which we have already noted, that the blood-pressure must be considered to provide a

factor which, if not quite negligible, is certainly of minor importance in causing a separation of the elements of the vessel wall. We have already referred to the observation that *even in a large-sized and thick-walled vessel*, where the fluid infiltration of the wall has been associated with a detachment of all the structures save the endothelial layer, the very fine film left behind is sufficient to resist the intravascular pressure. This point is well demonstrated in Fig. 29.

That the vacuolation of the endothelial cells is to be looked upon, not as an indication of an activity of cells specially differentiated for a secretory function, but rather as a condition merely incidental to the changes which are associated with the œdematous escape is demonstrated by the discovery of an exactly similar phenomenon in the connective-tissue cells of the vessel wall and the surrounding area of the tube through which they course. This remarkable condition, which has been merely touched on in a preceding section of this investigation, has been intentionally held over for a fuller discussion in the present place.

As already noted, the presence of a developing ovum in the tubal wall is associated with a degeneration of the muscular fibres. This is most evident in the immediate vicinity of the fœtal structures, and is, on the whole, the more widespread throughout the tubal wall the older the embryo. In its earliest stages these changes consist in a swelling of the substance and nuclei of the fibres, with a coincident diminution in their staining powers. With an advance of the process the cell boundaries become obscured and ultimately lost, and the fibres fuse with one another to form a structureless fibrinous material. Later there occurs a disappearance of this substance. *Pari passu* with these changes there is a progressive disintegration and ultimate disappearance of the nuclei. These degenerative alterations, though by no means confined to the proximity of the fœtal elements, are here most evident. In some cases the uniformly stained, degenerated material on section exhibits under the microscope an appearance strongly suggestive of opaque glass. In my sections these are the muscular changes invariably present; in none, even the youngest, is there any evidence of a muscular hypertrophy such as is found in the uterus during pregnancy.

Changes in the Connective-Tissue Cells

In marked contrast with these changes in the muscle is the condition of the connective-tissue cells of the tubal wall. As has been already

mentioned, scattered irregularly throughout the tube wall, the connective-tissue cells have enlarged in a manner closely resembling the decidual increase in the stroma cells of the uterine mucous membrane. Even where this alteration has not occurred to such a definite extent the connective-tissue cells are, however, for the most part somewhat enlarged. But what is even more characteristically detected is the fact that *the nuclei have preserved their structural appearances and staining properties, sometimes to a degree almost complete, and this even in these regions where the muscular disintegration has occurred to the most marked degree.* This observation, which I have been able to note in all my specimens which are sufficiently well preserved for a satisfactory histological study, would indicate that in their reaction to the fœtal cells, whatever this may be, the two main structural constituents of the tube wall, namely the muscle cell and connective-tissue cell, exhibit markedly varying degrees of resistance. Whilst the former quickly undergoes a progressive disintegration and ultimately becomes unrecognisable as such, the latter tends to persist and often preserves its identity throughout. In Plate VII. are seen vessels embedded in a medium composed of degenerated muscle; the surrounding connective cells are seen to be wonderfully well preserved.

But there is, in relation to the connective-tissue cells another fact of great importance, and one which especially interests us at present in our endeavour to show that the histological changes which we encountered in the endothelial cells are not to be looked upon as indicating changes necessarily dependent on a specific secretory function. This fact is found in the observation that *the fluid imbibition and swelling of the cells lining the vessels, to which attention was directed on a preceding page, are exhibited in precisely a similar way by the connective-tissue elements.* In all my specimens there is evident a marked degree of fluid imbibition by and distension of the connective-tissue cells in the tubal wall. In some sections this condition is exhibited by the majority of these cells, in other regions it is present only to a minor degree. It is invariably detected in the connective-tissue cells in the proximity of the ovum, where the tissues are markedly infiltrated with a fluid exudate, so also in the œdematous tracks round and in the walls of softening vessels. Even in the extremely degenerated structures immediately bordering on the intervillous space the process is often well marked. It is always visible throughout the tube at a long distance from the fœtal structures.

The description of the process as detected in the endothelial cells

applies with equal force to the changes exhibited in the connective-tissue cells. The affected cell becomes swollen up with a clear fluid, the cell substance becoming displaced to the periphery of the cell, often as a fine film, which in well-preserved specimens is often easily seen. The appearances produced by the cellular changes are many and various. The vacuoles may be small or large. In the former case the cell substance is seen as a distinct envelope round the imbibed fluid, in the latter case the cytoplasm may be represented by a mere film, which in some cases has disappeared, and the remaining portion of the cell, or perhaps only the nucleus, appears to lie in a clear space in the tissue (Fig. 42, and Plates VII. and VIII.). In some cases the resulting appearances might warrant the idea that the clear spaces have been produced by a shrinkage of the cells contained, and that in reality the changes described are not dependent on an intra-cellular fluid collection. That this, however, is not the true explanation of the changes is proved without doubt by the observation that it is often easy to trace, as already mentioned, the cell substance as a complete envelope round the vacuole.

The fluid vacuoles are, for the most part, chiefly disposed and reach their largest size in the neighbourhood of the nucleus. Where the connective-tissue cells are drawn out—and this is the shape mostly assumed by the altered cells — the vacuolation, however, may be present at any part of the cell substance, even at a distance from the nucleus. This may be encountered even in the fine filaments into which the cell substance is frequently drawn out. In these cases the appearance produced is that of a beadlike swelling in the course of the cell. In such cases the main portion of the cell protoplasm is usually involved in the process; in other cases the entire or the greater part of the length of such an elongated connective-tissue cell is occupied by a drawn-out, clear, fluid track. In many cases it is easy to trace such a track without interruption into a corresponding space in an adjoining cell. The rationale of this is easily understood by the fact that the connective-tissue cells are intimately connected, by means of protoplasmic outrunners from their bodies, with adjacent cells. This permits of the establishment, by the fusion of vacuoles which develop in the intervening cell bridge, of a continuous fluid track extending from cell to cell. In some cases it is possible, in the same section, to trace such a canal through three, four, or even more cells. Where cells lie side by side, with their long axes more or less parallel, there may be a disappearance of the intervening cell walls, with the production of a

fluid space lined by two cells (Plate VII.). This process may continue until ultimately a large œdematous space is formed which is lined by a considerable number of cells. These processes are easy to detect; their importance will be more fully related when we come to investigate the manner in which the sinus-like blood spaces and new capillary vessels are formed. When the vacuole of the cell reaches any size it is usual to find that the nucleus is drawn out and elongated in the direction of the long axis of the vacuole.

In Fig. 42 and Plates VII. and VIII. are shown a few of the variegated changes in contour, some of them very bizarre in nature, which the cells may present as the result of this vacuolated condition. Many of the appearances are artificial, and are due to the direction in which the section has been carried across the cell. For example, where the cell is cut across transversely through the level of the nucleus, the well-known "signet ring" appearance is produced. At one pole is the nucleus, and extending round and enclosing the fluid there is the attenuated film formed of the displaced cell protoplasm. Again, where the vacuolated cell is cut across obliquely the cell substance may appear to project as two horns from the end of the cell, which pass completely or only partly round the clear space. In this case we obtain the appearance often seen in the typical fibroblast. In the vacuolated spaces of the connective-tissue cells it is often possible to detect red blood corpuscles. This fact will be more specially referred to in a section devoted to the description of new vessel formation as seen in the pregnant tube.

We have seen that the fluid accumulation in the vessel walls, which usually commences on the internal aspect, and which, by its increase, ultimately results in a complete severance of the vessel confines, is determined by some tissue alteration which leads to an active fluid imbibition. The œdematous collection occurs under a hydrostatic pressure higher than that exerted by the blood against the vessel wall, and is so considerable as to lead, in many instances, to a detachment and projection into the vessel lumen of the inner layer or layers of the vessel wall. In the earliest stage it is represented by a fluid distension of the endothelial cells. The fluid thus confined within the individual cells soon bursts its bounds and escapes, first into the next portion of the vessel wall and thence through the succeeding layers till it ultimately reaches the surrounding tissues, which become ploughed up in the process. In the involvement of the vessel wall the process may be represented by the fluid spaces in the extracellular tissue, or it may, as in the endothelial layer, be represented by a hydropic accumulation actually

in the connective-tissue cells. The same applies to the surrounding tissues. When the loosening of the vessel wall has occurred to the extent of creating a complete breach in its continuity, and in the case of the thicker vessels, at any rate, not till then, we have an escape of the corpuscular elements of the blood into the surrounding tissues. It is important to note that, although in the smaller vessels there may be the occurrence of an extensive perivascular hæmorrhage before the surrounding tissues have been seriously involved in the œdematous escape, in the thick-walled vessels, on the other hand, there usually occurs a wholesale displacement of the surrounding tissues by a watery discharge before the blood cells leak out. In some cases the vessel may lie in a large clear space formed by a wholesale displacement of the surrounding tubal tissues, and yet the loosening of the vessel wall has not taken place to the degree necessary before there can occur an escape of the red cells.

We thus observe that the amount of the fluid escape varies within very wide limits. We have noted that in the vessel wall and in the surrounding tissues it may be represented by small clear spaces. From the smallest fluid accumulation we can distinguish all grades up to the very largest œdematous tracks in the tubal wall.

To resume the argument—we have been enabled, as the result of the study of the histological changes present in the vessels and the tissues of the pregnant tube, to dispose, in the first place, of a direct cellular trophoblastic invasion, and, in the second place, of a softening and mechanical filtration or a mere passive displacement as explanations of the manner in which the vessel walls become teased out and ultimately completely detached, permitting of a free escape of the contained blood into the surrounding tissue spaces, or, in the case of the vessels immediately apposed to the gestation sac, into the intervillous space. We were then able to discover that a "vital" or secretory fluid transmission on the part of the endothelial cells fails to explain all the phenomena, and we were reduced, in our quest after the secret, to tissue changes as the only possible solution of the problem. We have seen that the fluid is drawn into the tissues where it accumulates under a tension greater than that in existence in the corresponding blood-vessel. The tissue changes induced coincide with these which we associate with hydropic degeneration elsewhere.

Significance of Tissue Changes in the Production of the Œdema and the Hæmorrhage

What conditions determine the accumulation of fluid in a cell or in

tissues under a tension greater than is attributable to a mere passive escape from the neighbouring blood tracks from which the fluid is derived? If we turn for assistance in answering such a question to a modern text-book of pathology, we shall gain some information of importance. Adami (*The Principles of Pathology*, Vol. I., 1909) defines hydropic degeneration as "the appearance of definite vacuoles in the cytoplasm, containing a watery fluid, which vacuoles may attain so great a size that the cell undergoing disorganisation bursts, and with its neighbours becomes represented by a vesicle visible to the naked eye." In this description of the process we recognise a close resemblance to the changes which we have noted in the vessels and tissues of the pregnant tube. Adami goes on to say that "this rapid imbibition and accumulation in a cell can, upon physical grounds, have only one explanation. The constitution of cytoplasmic matter, as also of the nucleus, is colloidal, and colloidal membranes (for such we can regard the surface layers of cells) have characteristic properties. They hinder the diffusion of crystalloid molecules to a considerable extent. Although animal cells possess no well-formed outer membrane (as do plant cells), we are led to believe that in animal cells a fine layer of similar nature acts physiologically as such a membrane. We therefore conclude that the essential cause of hydropic degeneration is some dissociation of the complex colloid material of the cytoplasm, whereby, either by cleavage or ionisation, crystalloid bodies make their appearance in the protoplasm. As an illustration of conversions of this order, it may be noted that the peptones, leucin, tyrosin, etc., which are the products of the breaking down of (colloidal) proteins, are of distinctly crystalloidal nature. So long as such products are present within the cell body in greater concentration than they exist in the surrounding medium, there will be tendency to osmotic diffusion inward of watery fluid until such time as the osmotic pressure on the two sides of the membrane becomes equal. In other words, the cell swells up and becomes hydropic."

If the conclusion to which our investigations have carried us be correct, and I maintain that no other explanation accords with the ascertained facts, we must look to some protoplasmic change similar in nature to that which is described in the above passage for the key with which to unlock the secret of the fluid transference from vessel to tissue as it is encountered in the pregnant tube. By this means, and by this means alone, can we satisfactorily explain the fluid imbibition and distension of the endothelial cells and of the connective tissue cells, the first of which we invariably detect, and the latter whenever

the tissue destruction is not too extensive. By this means we procure, further, an explanation of the fluid aeeumulations so richly seattered through the affeeted tube, where the eondition is distinctly due to a bursting of the walls and amalgamation of such distended eells. As has been shown in the preeeding ehapter, and as will be more fully described on subsequent pages, reeent researeh would indieate that simple osmotie processes, as reeognised in the laboratory, fail to embraee all the phenomena of œdema produetion. While this is so, it in no way affects the legitimaey of the main eontentions whieh I propose to advanee. So long as we are uneertain of the exact nature of the changes in the colloids of the tissues whieh enhance their affinity for water, the word "erystalloid" must be eonsidered as synonymous with "altered eolloids with an inereased attraetion for water."

Does this faetor, namely, a diffusion from a place of lower to one of higher erystalloidal eoneentration, amply account for the fluid aeeumulations, whieh, so far as we can see, are purely extraeellular in their position, and whieh in some instanees attain huge dimensions? Sueh a fluid eolleetion we have deseribed as frequently, espeeially in the early stage of the œdematous teasing out of the walls of a well-supported vessel, leading to a wholesale floating-up and projeetion into the lumen of the endothelial sheet. This eondition is found espeeially in those vessels where the immediately adjacent portion is wholly or only slightly involved in the proeess. The change in sueh a ease, whilst in all probability initiated by an active aceumulation in the individual endothelial eells, must, by the time it has reaehed this stage, be due to an œdematous collection, for the greater part eompletely external to the cells and not to an amalgamation of a large number of eells eaeh exhibiting the change. What these appearances teach us is that the eseape of fluid can lead to the produetion of, and ean oeeur into, large spaees ereated in the tissues without the intervention of obvious cellular ehanges. In this ease the eolloidal membrane necessary for the proeess has been furnished by the endothelial sheet. As we have repeatedly noted, this struetural alteration in the vessel wall is rarely limited to its endothelial aspeet. In most eases it is quickly followed by a similar œdematous aeeumulation in the immediately external part of the wall, which in many instanees is separated by a fine tissue partition from the inner fluid-distended spaee. This film of tissue intervening between the two dropsical eavities, which in many cases is in the pregnant tube nothing more than a greatly degenerated portion of the vessel wall,

appears to act, like the better preserved endothelial sheet, in the capacity of a colloidal membrane, which, while retaining the crystalloids, determines the diffusion of fluid from one space to the other. In such a case, again, the process would seem to have occurred without the medium of an actual intracellular accumulation. In this case we have again to deal with a passage of fluid from one region of lower to another of greater crystalloidal concentration. And so on the process extends till, even in the case of a thick-walled vessel, the entire wall becomes teased out, and the surrounding tissues become directly involved. That an explanation of this nature must be the true one is evidenced by the fact that where the tracks thus successively created become continuous by a disappearance of the intervening colloidal partitions, the contained fluid is seen to be under a hydrostatic tension in excess of that exerted by the lateral pressure of the blood in the corresponding vessel. This fact we have conclusively demonstrated in a preceding part of this research.

The manner in which the colloidal partitions give way is intimately bound up with one of the most characteristic vessel and tissue changes detected in the pregnant tube. We have already observed that in addition to mere displacement of tissue *there has occurred in many places a marked solution of tissues.* This especially involves the degenerating muscle, in which one can often see a wholesale disappearance of the muscle fibres, which apparently become transformed *en masse* into soluble ingredients which pass into solution in the fluid absorbed.

The fluid escape from the vessels does not always follow on lines associated with such gross microscopic changes as those described above. In Plate VI. is represented a fine-walled vessel, from which there is occurring this dropsical infiltration. On the inner aspect we see the hydropic changes in the endothelium to which we have frequently referred. The fluid imbibition has here and there round the vessel circumference led to a detachment and bulging of several of the lining cells towards the lumen. The underlying fluid accumulation is well seen on the lower aspect of the plate. That this has been formed by diffusion through the endothelial sheet must, I think, be freely admitted. Besides the definite evidence of the fluid interchange, as demonstrated by the endothelial vacuolation and the sub-endothelial spaces, the immediately subjacent part of the tube, which in this case is formed, not by the structures of the vessel, which is possessed of only an endothelial layer, but by the tissues of the tubal wall, is seen to be thickly studded with clear spaces of varying size. The fact that these

spaces can often and with ease be traced directly into the sub-endothelial region proves beyond a doubt that their contained fluid has accumulated under a tension considerably greater than that of the intravascular pressure. In other words we learn that the passage of the fluid into the tissues of the tubal wall is established by a process of imbibition, and must be dependent on some tissue changes.

The giving way of the tissue partitions between the fluids in two spaces formed in the above-mentioned way may be explained by purely mechanical influences. As can easily be understood, the fluid in its passage across the membrane may accumulate in one of the cavities to such an extent as to thin out and rupture the intervening septum. Into the common space thus produced, in which the crystalloidal content may be still high, there may, however, be further diffusion of fluid from a region of greater dilution, *e.g.* the blood. Whilst such a mechanism would furnish an explanation of the disappearance of the intervening septum, it is possible that the real explanation is to be found in the structural nature of the partition. This is not, as in the case of the colloidal membrane employed in experimental research, a structure which remains unchanged except for the mechanical displacement which it exhibits when the tension on one side exceeds that on the other, and which, when this pressure discrepancy is sufficiently great, might be conceived to rupture. In the case at present under discussion we are dealing with a tissue which can itself become teased out and disappear in response to the same process which has determined the fluid transference through it. If we can assume, which I think is not unreasonable, that the tissues within a small area are charged to a like degree with crystalloids liberated by protoplasmic changes induced by the chorionic activity, we can see that a continual passage of fluid from lower to higher "osmotic" levels is efficiently maintained until the tissues are saturated, for the portion first involved by the fluid ingress falls in osmotic pressure in proportion to the amount of fluid entering, and this establishes a pressure discrepancy between it and the adjacent tissues, which determines a diffusion across the colloidal membrane, and so on till large œdematous areas are produced. The fluid tracks thus produced gradually, and more or less uniformly, widen their circumference, the increasing fluid necessary for the process being derived from the blood-stream, which is depleted to a corresponding extent.

As we have seen, the above process results in many cases in a wholesale opening out of the structures forming the vessel wall, and this even in those cases where this is thick and well supported. Whilst

these changes are most manifest in the vicinity of the chorionic structures, they are nevertheless still evident, and in the case of the older embryos often to a marked degree, at a distance from the ovum bed. In one case the changes were detected in large, thick-walled vessels towards the inner end of the tube, which contained a growing ovum in the ampullary portion.

It seems certain that the displacement of tissue which occurs in the tube during pregnancy is too extreme in degree to be attributed to a mere mechanical infiltration of fluid through the vessel walls. It is often possible to recognise a wholesale displacement and separation of the muscular tissue of the tube wall even when the bundles exhibit little evidence of degenerative softening. The fact, moreover, that even where the process has resulted in a complete teasing apart of the vessel wall the fine endothelial pellicle may remain perfectly intact, would tend to indicate that intravascular pressure plays a very unimportant part in the production of the changes encountered. In the case of the vessel where there is produced clear tracks from endothelium to tissue the osmotic flow may have been a gradual one, first through vessel wall with a successive detachment and separation of the tissues, which have in their turn acted the *rôle* of colloidal membranes, until ultimately the fluid, still diffusing into realms of increasingly high affinity for water, reaches the surrounding tissues, where the same process proceeds. Here it may progress to the extent of completely separating the vessel from the neighbouring structures. This, as has already been mentioned, is rendered the easier by the softening and degeneration of the tissues which occurs in the pregnant state.

Whilst it is easy to trace the various steps in the process just described by which the fluid stream traverses the vessel wall in its passage to the tissues, it would seem that this description does not embrace all the facts. In the above-noted process it was observed that the fluid leaks by well-defined stages through the vessel wall, each part of which, after assuming in its turn the function of the colloidal membrane, gives way, and a track is thus produced by the gradual teasing out of the wall which conveys the fluid to the tissue. This channel may be complete or it may be interrupted by parts of the vessel wall which persist. In other cases, however, there may be a wholesale escape of fluid through a vessel which exhibits the above changes in only a very small degree or not at all. In such a condition, which is usually associated with a well-supported wall the structures of which are too closely knit together to become detached in the above

manner, the entire thickness of the wall has functioned as the colloidal membrane, separating the regions of comparatively low affinity for fluid (the blood) from the regions of high crystalloidal concentration. In such a case the conditions, although identical in their fundamental nature with the above-mentioned process, conform more closely to the conditions in which the phenomena of osmosis are studied *in vitro*, the thick-walled vessel in this case corresponding to the animal membrane employed for the experiments.

Whilst the facts are explained only by a description such as that given, it seems not unlikely that, with an increase in our knowledge concerning the laws of fluid interchange between blood and tissue, the explanation advanced above will require some re-adjustment. More recent research would tend to indicate that the conception, which we have derived from experimental investigations, that osmosis consists in the diffusion of fluid across a definite and unchanging colloidal membrane into a space containing a simple solution of crystalloids, must be modified when applied to living matter. In a recent article on the "Equilibrium of Colloid and Crystalloid in Living Cells" Benjamin Moore[1] says: "The whole chemical structure of the cell and that part of it which is physiologically active is the osmotic machine, and needs no membrane permeable or impermeable in order to exhibit the usual osmotic phenomena of shrinking or swelling, leading finally to disruption . . . in all cases the nature of the bioplasm is so differentiated chemically as to form a dividing surface readily permeable to the solvent, and this is all that is required, in addition to the varying unions or holding powers between the cell colloids and crystalloids, to establish an osmotic cell. As an example of what is meant here we may instance the swelling of fibrin, connective tissue, and gelatine under the imbibition of water. Between gelatine and water there is no structural membrane with semi-permeable pores, yet the gelatine takes in water in a truly osmotic fashion, and the pressure developed, if the swelling and uptake of water are resisted, is very high." If, instead of the idea which demands the existence of a definite colloidal membrane, "we take the view, which is supported by experimental facts, that the bioplasm holds the crystalloids in loose union in the cell, so that they cannot for the time escape or diffuse out, and yet admits of a degree of molecular freedom to the crystalloids, so that they still attract water molecules by residual affinity, then we arrive at a conception which is capable of linking together the osmotic properties of the cell, not merely in a

[1] *Further Advances in Physiology*, Arnold, 1910.

statical but in a dynamic way, and gives a basis for understanding the variations in osmotic effects which accompany cell activities from one phase to another."

One point especially demands further study, namely, the exact manner in which the osmotic relations of the tissues are altered by degenerative changes in the cell protoplasm, such as that induced throughout a large extent of the tubal wall in the case of a pregnancy in that region. Whilst we have seen that in many places the phenomena, as seen in the fluid imbibition and distension of the cells, accord with the well-known effects of osmosis in other regions, we have been compelled to introduce a similar explanation to meet the changes induced in the parts of the wall where the cellular characters are lost, and where the tissues are, in many instances, represented by a homogeneous fibrinous material. It would seem not unlikely that, under the chorionic influence, the degenerative changes exhibited by the more susceptible elements of the tubal wall—and this, as we have seen, applies to the muscular tissue—have been associated with an alteration in the colloids in a way differing not so much in nature as in degree from the more resistant endothelial and connective-tissue elements. In a subsequent section of this research devoted to the study of the changes induced in the wall of the uterus by chorionepitheliomatous masses I shall demonstrate that in the degenerating muscular tissue there is indisputable evidence of an active fluid imbibition such as probably occurs in the pregnant tube (Plate XIII.). We have seen that throughout the pregnant tube the endothelial and the connective-tissue cells are greedily imbibing fluid from the blood tracks, and this last observation would indicate that the only other structural element of importance, namely the muscle, is in all likelihood undergoing the same change.

In this connection it is interesting to note that recent research into the activities of the placenta has suggested the existence, amongst others, of a proteolytic ferment which leads to the conversion of proteins to peptones. The importance of this in relation to the present research is that we have an experimental explanation of the changes in the tissues which our study of histological alterations has led us to adduce. This is found in the fact that the digestion of proteins results in a production of substances (peptones, etc.) with an enhanced osmotic tension. Be this as it may, and it must be admitted that the nature and mode of action of the placental ferments are still under dispute, the fact that all round the fœtal elements the maternal tissues, and especially the muscle, are undergoing active disintegration would suggest strongly the existence

of some substance liberated by the chorionic cells. Wherever these touch the maternal tissue there is an immediate destruction, and the absence of any phagocytosis would indicate that the ready disappearance of the muscular substance, etc., is due to an extracellular material derived from the fœtal epithelium, which breaks up the protoplasm with which it comes in contact into soluble elements.

Explanation of the Blood Escape from the Vessels

I have indicated that the teasing apart of the vascular walls often, especially in the neighbourhood of the chorionic structures, results in the production of a breach or wholesale gaping through which there ensues an escape of the blood corpuscles. This change, we have also noted, is readily discovered in the wall of the pregnant tube, even at a considerable distance from the ovum. In the proximity of the gestation sac this process is, as we have seen, in all probability responsible for the opening of the maternal vessels into the intervillous space and the provision of a necessary blood supply for a developing fœtus. Whilst most marked in the case of the smaller vessels, the blood escape thus induced is, however, often detected in the thick-walled vessels. In different parts of the same tube, like the dropsical infiltration, it is, on the whole, in amount inversely proportional to the distance from the site of the ovum. In different tubes, again, the degree in which the hæmorrhage is encountered is, for the most part, proportional to the age of the ovum.

The mode in which the blood escape occurs is easily understood by recalling the way in which the œdematous infiltration results in a detachment of the structures forming the vessel walls. As we have seen, this often occurs to the extent of producing a direct communication between vessel lumen and tissue spaces, along which the red blood corpuscles are streaming. If the process involves the entire circumference of the vessel wall, as is frequently the case in the immediate proximity of the intervillous space, there occurs a wholesale hæmorrhage into the surrounding tissues, the corpuscles streaming out in all directions (Plate V.). The exact manner in which this occurs is not difficult to understand in view of the previously recorded observations. On Plate VI. is shown a vessel at a little distance from the fœtal elements, through the walls of which there is occurring a passage of fluid from lumen to tissue in the manner described in the preceding pages. This is occurring round the entire circumference of the vessel, and has led to the production, in the wall and in the surrounding tissues, of fluid spaces and tracks. The vessel cavity is still shut off by the endothelial

layer. It is clear that the removal of this (and how this probably occurs I have already indicated) would result in a passage out of the red cells. If the fluid is still being drawn into the tissues, it is obvious that the red corpuscles will be dragged out just so far as the process of disintegration has led to the creation of an uninterrupted track. That this does actually occur is demonstrated by the discovery in the nearer proximity of the ovum of the corpuscular elements streaming into these tissue spaces.

Whilst it is easy to understand, in this way, the rationale of the blood escape into the immediate proximity of the vessels, what factors are responsible for the transference of the blood elements into more distant regions of the tubal wall? As has already been mentioned, it is often possible to detect, especially in the neighbourhood of the ovum, a track of hæmorrhage extending through the tubal wall for a long distance from a vessel (Plate V.). There would seem to be two possible explanations of the manner in which this blood stream takes place. In the first place it is possible that, subsequent to the teasing out of the tissues with the establishment of a continuous track leading from the vessel interior, the stream is determined by the force which is responsible for the flow along the vessel under ordinary circumstances. In addition to this *vis a tergo*, however, it would seem highly probable that there enters into the process a *vis a fronte*, in the shape of the tissue changes which, as we have learnt, are drawing on the fluid from regions of lower to regions of higher fluid attraction. The relative importance of these two factors we are unable to determine with accuracy, though it would seem highly probable, from the researches recorded in the preceding pages, that the latter factor must assume a part of not inconsiderable importance. On the other hand, it is clear that whilst it is feasible to imagine that this force might alone carry the blood to the surface of the fœtal chamber, for the completion of the process, namely a flowing of the blood into the intervillous space, the first factor would seem to be essential. Though this is the case, I shall subsequently adduce evidence in favour of the idea that the fluid absorption by the fœtal structures may, to some extent, aid in drawing the blood through the superficial maternal tissues.

We have repeatedly referred to the fact that whilst these vascular changes are exhibited in varying degrees throughout the wall of the pregnant tube, that portion which borders on the gestation sac is almost invariably seen to be extensively infiltrated with red corpuscles which are seen to be escaping in large numbers through the walls of vessels

in this region which have not yet completely given way (Plate V.). Another fact of considerable interest and importance which is observed in this region is that the walls of the vessels concerned are often seen to be most involved in the process on that aspect which faces towards the surface of the fœtal advance, and whilst the chorionic cells are still at a considerable distance. These facts coincide with what I have previously referred to, namely, that the extent to which the vessels are involved reaches its maximum in the fœtal neighbourhood, and they, moreover, tend to indicate what we should expect, that the tissue changes induced by the growing ovum are of such a nature as to determine in the region of the intervillous space a flow of the constituents of the blood towards the region of the chorionic advance. If our interpretation of the phenomena, then, be correct, we are furnished with evidence which justifies the conclusion that the object of the complex vessel and tissue changes which we have studied in the preceding pages is the provision of a liberal supply of maternal blood for the engrafted ovum.

Significance of a Direct Infiltration of the Vessel Walls by the Chorionic Cells

The investigations recorded in the preceding pages have indicated that the orthodox conception regarding the manner in which the blood supply of the fœtus is obtained must be modified. There is in action some process other than an invasion and destruction of the vessel wall with a mechanical liberation of the contained blood. That this is not essential to the process is strikingly demonstrated by the fact which I have described, that the blood can often be seen streaming from the vessel towards the intervillous space when the fœtal cells are still at a considerable distance.

On the other hand it is often possible to detect a direct infiltration and destruction of the vessel by the engrafted cells. What is the significance of this? Such a vessel is represented in Fig. 27. At one part a villus is seen incorporated with the vessel wall, the tissue of which has been to a large extent removed. Some of the chorionic cells have extended as far as the endothelial layer. The wall in the neighbourhood is œdematous and is infiltrated with blood. The muscular tissue is disintegrated, and has, for the most part, disappeared, apparently having entered into a state of solution. It is obvious that here the changes are identical in nature with those seen at a distance from the fœtal cells. The difference is one of degree only, being more marked here because of the proximity of the cells. In another part of the

vessel wall (below in the figure) there is seen to be a greater destruction, and there is seen to have been produced a distinct communication between vessel and intervillous space at the side of the invading villus. Here the tissue removed is, as is often noted, in bulk greater than the chorionic mass; this is clearly dependent on the dissolving process to which I have repeatedly referred.

The appearances produced, therefore, correspond accurately with those encountered throughout the marginal area of the ovum bed. The corrosion of the vessel walls by the direct chorionic invasion is to be looked upon not as the essential factor in the liberation of the maternal blood but rather as an incident in the process by which the tubal wall is uniformly involved. So far from its being correct to state that the blood cannot escape till the chorionic cells directly invade the vessel wall, the reverse is the case. The chorionic cells are actually seen to be burrowing through the tissue towards the vessel from which the blood is already escaping. In so doing they would seem to be developing most in that direction from which their nutrition is flowing. If our interpretation of the process be correct, then, we are in this region brought face to face with a remarkable cycle of events. The chorionic substance passes into the tissues, which become chemically altered and respond by actively imbibing the blood (fluid and corpuscles). This will tend to pass in the direction of the greatest tissue change, *i.e.* towards the fœtal cells, and this tendency will be assisted by the active fluid absorption on the part of the fœtal elements. These naturally develop most on that aspect facing the direction of the nutritional flow, and they therefore grow towards the vessel, the walls of which they ultimately reach, with the results I have recorded. In Fig. 27 it is seen that the vessel wall is becoming teased out on the side most distant from the chorionic invasion, a condition which is not difficult to understand in view of the ready way in which the fœtal extracellular substance spreads through the tissues.

The passage of the blood towards the chorionic cells is also facilitated by the vascular expansion which is occurring. This, it is easily seen, must tend to transport the blood *en masse* towards the chorionic site.

Whilst in the neighbourhood of the chorionic cells the destructive changes dominate the process, this is by no means invariably the case. Whilst the muscle early disintegrates, there is often, as I have mentioned, a persistence of the endothelial and connective-tissue elements. Not only so, but there may actually be found evidence of a definite reaction in the elements in the shape of a new formation of blood-vessels. This

obviously will serve the purpose of conveying the blood in the direction in which it is required. This again, as I shall show, is merely an evidence of the tissue changes referred to.

Mode of Formation of Blood Sinuses in Tubal Wall

As has been mentioned before, there is found scattered about the wall of the pregnant tube a considerable number of large, thin-walled blood spaces or *sinuses*. These consist, as in other regions, of distended blood tracks, whose walls are formed by a single layer of endothelium. In the tube they are found more especially towards the peritoneal aspect. They exhibit great differences in size, varying from channels whose walls on section are formed of three or four cells to large, greatly-expanded blood lakes. As they would seem to correspond to the blood sinuses which develop in the endometrium and in the muscular coat of the uterus during pregnancy, it was thought that a study of their mode of formation might cast some light on the process at work in the case of the uterus.

In shape they exhibit wide variations; some are more or less circular or oval, whilst others are drawn out and may extend for a considerable distance through the tubal wall. These differences may, to some extent, depend on the plane in which they are cut across in the sections. In most cases they do not, however, possess such a regular contour. Their boundary is usually irregular in shape, sometimes to a remarkable degree. From the main channel arms or branches of varying size are projected into the wall of the tube. In many cases the tracks are tortuous. The appearances exhibited suggest strongly that the sinus-like space once formed continually increases in size at the expense of the adjacent tube wall. In the extension of their boundaries they are often seen to pursue the line of least resistance. They are, for example, often seen to skirt bundles of muscle which are interposed in the path of their advance. In many cases the off-shoots are seen to burrow along between two such muscle bundles. In fact, the appearances revealed indicate that the surface irregularities are dependent almost entirely on such influences. In the unevenness of their boundaries these sinuses coincide with the similar spaces in the pregnant uterus (Figs. 40, 41, and Plates VII., VIII.).

It would seem that the large blood spaces must be formed from pre-existing vessels, and the structure of their wall would seem to warrant the conclusion that they are developed, for the most part, from capillary

vessels. There are no structures in the normal tubal wall in the least corresponding to them in dimension. Their origin is also indicated by the fact that it is sometimes possible to determine the existence of a fine capillary connection between two adjacent spaces which then simply look like two enormously distended regions of the same blood track. It will be pointed out, however, that even thick-walled vessels may assume like invasive properties when deprived of their investing and supporting muscular coat.

How are they formed? The fact that with an increase in size there is a corresponding increase in the number of the cells forming their wall indicates that they are not formed by a process of mere mechanical expansion. The fact, moreover, that although there must be a rapid increase in the circumference of the wall there is in none of my specimens any evidence of a division of the component cells, would suggest that there is something more than an increase in the pre-existing lining cells. I would advance the following observations in support of the fact that in the process of expansion the walls are continuing coming into line with, and embracing, the adjacent connective-tissue cells of the tubal wall.

It has already been mentioned that in many of the sections there is seen a process of fluid imbibition by the connective-tissue cells. This is associated with the formation of vacuoles, often of large size and sometimes several in number, within the cell body, the protoplasm of which is displaced to the periphery. The many and varied appearances exhibited in the process of the fluid distension of the cells have been described on a former page. It was also observed that where two such cells lay close together there was often noted an amalgamation of the fluid space permitted by a disappearance of the intervening cell protoplasm. Where this occurred in the case of two or more cells lying end to end there was produced an elongated fluid track which in many instances could be traced through three or more cells in the same section. Where the cells lie side by side the disappearance of the separating films of cell substance results in the formation of a more or less circular space filled with clear fluid bounded by two cells. The various stages in this process are easily traced. By amalgamating with an adjacent, similarly distended cell we have the production of a space formed by three cells, and so the process would seem to be capable of extending till a large space may be created (Plates VII., VIII., Fig. 42).

It has already been noted, also, that these changes in the connective-tissue cells which are dependent on alterations in their protoplasm are exhibited in a manner exactly similar by the endothelial cells of the

blood-vessels, in fact that the process in each case is in the beginning determined by one common factor, namely the tissue changes caused by the presence of the growing ovum. Where a vacuolated endothelial cell abuts on a similarly affected connective-tissue cell which is placed more or less parallel to it, there is again apt to be an amalgamation of two spaces.

This appearance is often easily recognised in different parts of the circumference of such a sinus-like space. On Plate VIII. is shown such an expanding vessel; on the left lower aspect of this there is seen a connective-tissue cell coming into communication with the invading blood space. The disappearance of the fine film of the lining cell which separates the space produced by the union of the two vacuolated cells results in the extension of the blood cavity up to the level of the outermost cell. It can easily be understood that this process will lead to the steady expansion of the space. It can also readily be seen that any obstacle in the shape of a muscle bundle will effectually bar at that part the progress of the extension process and explains the rationale of the manner in which the expanding space skirts the muscle and sends an off-shoot between the two interposing bundles. Outward projections of the blood cavity thus produced often look like new blood-vessels, but their real nature is easily determined by tracing them by serial sections, when they are found to consist of *cul-de-sacs* (Fig. 40).

Although, for the most part, the formation of such sinuses would seem to occur chiefly from the finer vessels, it is interesting to note that the same process may be detected in the thicker-walled vessels. On Fig. 41 is shown such a vessel in which there has been a detachment of the investing muscular coat. The lining layer thus released is seen to be throwing out projections into the tubal wall in the manner described above. These look at first sight like parts of complete blood channels. On tracing by serial tracing they are found, however, to terminate blindly. It is interesting to note that in the vessel figured, as in many others, the projection into the surrounding tissues of the finger-like processes is occurring almost entirely in the direction of the growing fœtal cells. This is natural in view of the fact that the change is dependent on the fœtal influence. It is obvious that such an expansion of the vessel walls in the case of those vessels close to the fœtal structures culminates in a wholesale transference of the necessary nourishment towards the intervillous space. It will be subsequently pointed out that a process analogous in every respect may occur in the

uterine mucosa in the case of an ordinary pregnancy. I have pointed to a similar process in the menstrual mucosa.

Mode of Formation of New Blood-Vessels in Wall of Pregnant Tube

In places throughout the wall of the pregnant tube there is a new formation of blood-vessels. As in the case of the newly-formed blood sinuses described in the last paragraph, this process is most evident towards the peritoneal aspect of the tube, and, as a matter of fact, the two processes are often found occurring hand in hand. The formation of the new vessels is best studied round the circumference of the blood lakes. Here there is often detected a rich budding out of the wall in the form of fine capillary off-shoots (Plate VII.). Even in the case of a small sinus there may be found six, eight, or more such capillary off-shoots being projected into the surrounding tubal wall. In some cases these are found, on tracing by serial sections, to end blindly after running for a short distance in the tubal wall; in other cases they appear to extend through the tubal wall for a considerable interval, and they can be noted in many instances entering into an anastomotic communication with one another.

Whilst at first sight the mode in which new vascular formation takes place in the pregnant tube may seem to be irrelevant to the subject under discussion, its importance will be recognised when we come to the discussion of the changes produced in the uterine mucosa by the presence of the growing ovum. Round the periphery of the early blastocyst a formation of new capillary vessels has been noted in the young decidual membrane, and the investigations here recorded would seem to cast considerable light on the factors probably in operation in the case of the uterus.

I have already referred to the fact that in the fluid spaces in the substance of the connective-tissue cells it is often possible to recognise the presence of well-preserved red blood corpuscles. This fact would seem to provide a clue to the manner in which the new capillary off-shoots are formed. In the description of the vacuolated condition often exhibited by the connective-tissue elements it was mentioned that where two or three such cells lie end to end there is apt to be a running together of the fluid spaces with the creation of a track continued along for a corresponding distance (Plates VII., VIII.). In last paragraph, also, it was noted that where such a cell lay apposed

to a vacuolated endothelial cell there was noted in many cases an amalgamation of the two cells and a subsequent extension of the blood cavity to a corresponding degree. The new vessel formation would seem to be dependent on the same cause. Where a connective-tissue cell is set at an angle to a vacuolated endothelial cell there is seen a fusion of the fluid spaces, and with a disappearance of the film of cell substance intervening between this new fluid track and the vessel lumen there is produced a new capillary vessel.

Similar appearances are shown in Plates VII. and VIII., and throughout the tubal wall the vacuolated connective-tissue cells are seen. In the neighbourhood of the vessels these have served in the formation of the new capillary twigs. A point of interest is that an apparent projection of a solid bud from the endothelial layer is seen, on tracing in serial section, to consist, in reality, of a complete canal, the wall of which has merely been cut across at a tangent.

How is the disappearance of the cellular film which is essential to the process to be explained? It seems not improbable that this may be due to a mechanical yielding to the intracellular tension produced by the distending fluid. It may, on the other hand, be due to the dissolving process which is occurring, for it is often possible to detect a nucleus devoid of cell substance lying in a fluid space. The cytoplasm has apparently disappeared in solution.

It will then be seen that the two processes described in the last two sections of this research—the formation of the sinus-like expansions of the vessels and the formation of new capillary twigs from the pre-existing vessel walls—are to be traced to one and the same factor, namely an alteration in the cell protoplasm determining an absorption of fluid from the vessel lumen or the tissue spaces. This, we have seen, is in all probability to be explained by a change in the constitution of the colloids of the cell which leads to an increase in the affinity of the cell substance for fluid.

We have arrived, then, at a conclusion which to me seems to be of the greatest importance, namely that *the three changes exhibited by the vessels in the tubal walls are traceable to the same common factor.* We have already adduced evidence which proves beyond dispute that the dropsical infiltration and teasing asunder of the structural elements of the vessel walls, which is found to a marked degree in the pregnant tube, and which is more and more evident the nearer the engrafted ovum is approached, must be dependent on tissue changes which result in an active imbibition of fluid from the vessel lumen. We have now

advanced evidence which seems to indicate that in the expansion of the vessel walls and in the throwing out of the capillary twigs exactly the same process is in action, the only reservation being that in the two latter conditions the endothelial and connective-tissue cells alone share in the changes. Although the resulting changes in these conditions are so different, in their fundamental nature they are similar. The only difference is that whereas in the one case the blood fluid and corpuscles are drawn in an irregular and uncontrolled manner into the tissues, in the other case they are being drawn into further and further regions along definite intracellular channels, or they are carried out *en masse* by the expanding sinus.

If our interpretation of the phenomena be correct we have derived from our investigations information which tends to establish the *close structural relationship between endothelial and connective-tissue cells; this is found in the fact that the latter are able, under certain circumstances, not only to range themselves alongside and to take part in the formation of the endothelial layer of the expanding vessel, but they can also become canalised to form the lumen of a capillary vessel.* The observations just recorded will be seen to correspond in many points to the description given of the changes in the mucosa in menstruation. There the œdema and hæmorrhage took place in response to similar tissue changes. The new formation of capillaries which has been described in the menstruating mucosa by several observers would, in the light of the above investigations, find a ready explanation. I have already suggested that the tissue changes, which result in an active fluid imbibition, in all probability account for the sinuses which develop in the menstrual endometrium.

In this place it must be mentioned that the intracellular formation of capillary vessels has been repeatedly described by other investigators. All I claim for the observations here recorded is that, besides adding a contribution to the evidence in support of this conception, they would indicate that the rationale of the process is to be found in protoplasmic changes induced by some external influence which, in the case under discussion, is in all probability to be identified with the biochemical influence emanating from the chorionic cells.

Summary

(1) In the pregnant tube the extrachorionic influence of the fœtal cells leads to a marked degenerative change in the maternal tissues. This is most marked all round the marginal area of the

implantation chamber, but it extends for a considerable and varying distance beyond this. The furthest spread of the disintegrating changes occurs along the track of the veins. The maternal changes are due to some material which is liberated by the chorionic cells, and which spreads in increasing degree into the surrounding regions. In the maternal structures forming the confines of the ovum bed, and round the walls of the vessels near this, the disintegrating changes result in a wholesale splitting up and solution of the tissues, especially of thc muscle. This explains the manner in which the implantation chamber is formed, and also the way in which many of the blood-vessels invade the maternal tissues to form large blood tracks.

(2) The commonly accepted idea that the maternal vessels are opened up by a direct infiltration and destruction of their walls by the chorionic cells does not suffice to explain all the phenomena. The conception, also, that the opening up of the vessels is due to a giving way before the intravascular tension of vessel walls in the proximity of the intervillous space, which have previously undergone a degenerative softening, likewise fails to embrace all the facts.

(3) (*a*) In the tubal wall there is a widespread œdema and hæmorrhage. Whilst most marked in the vicinity of the chorionic elements, they are, however, present at a long distance from these. The loosening of the vessel walls is, for the most part, co-extensive in location with the region of the œdematous infiltration of the tubal wall.

(*b*) The cause of the opening out of the walls is a gradual separation and giving way of the tissues by the dropsical exudate. This, in the majority of cases, commences on the inner aspect of the wall and steadily progresses in an outward direction. In its most marked degree it results in a complete detachment of the wall and a wholesale escape of blood into the surrounding tissues or the intervillous space.

(*c*) The changes are manifest even in the thick-walled vessels, especially the veins.

(*d*) The œdematous escape determining the changes is not due to a mechanical displacement or filtration, nor is it due to a secretory activity on the part of the endothelial cells.

(*e*) The changes must be due to protoplasmic changes which are associated with the production or liberation of "crystalloids" and an increase in the affinity of the tissues for fluid. By the watery diffusion we have the transference of fluid into and through the vessel walls, leading to a ploughing up of the surrounding tissues to a marked degree.

(*f*) The "suction" of fluid into the surrounding region thus produced is associated, in the case of the vessels, where there is the creation of a complete breach in the wall, with a passage of blood into the surrounding tissues or into the intervillous space.

(4) In the wall of the pregnant tube an extensive formation of expanded blood tracks occurs. In the necrotic tissue this is dependent partly on a displacement and partly on a solution of the maternal tissue in the blood fluid. In other regions the blood spaces correspond to sinuses with a definite endothelial lining. There also occurs an extensive formation of new capillary vessels. These changes are especially evident in the fine-walled vessels. They may, however, be found in the thicker vessels after a detachment of the supporting coats. In the vicinity of the ovum both changes assist in carrying blood towards the fœtal cells. The vascular expansion and new formation are due to the same tissue changes as determine the generalised œdema and hæmorrhage.

CHAPTER IV

THE EXTRACHORIONIC ACTION OF THE FŒTAL CELLS ON THE MATERNAL TISSUES (*continued*)—PLACENTAL FRAGMENTS AND CHORIONEPITHELIOMA

Changes in Uterus in Retained Placental Fragments

For this investigation I have been able to procure only one specimen. It consists of an entire uterus removed by vaginal hysterectomy, to the anterior wall of which, near the fundus, a small fragment of what at first looks like ordinary blood clot is adherent. On section the clot is seen to be sharply cut off from the adjacent paler muscular tissue of the uterine wall. This projects as a distinct polypoidal swelling into the uterine cavity at the point of attachment of the clot, and in it a number of dark red patches are seen. These, as will be shown subsequently, correspond to greatly distended blood spaces. The clot measures ½-in. wide by about ¾-in. in length. The mucous membrane of the rest of the uterus is deeply congested. All the history of this specimen that I can give is that it was obtained from a woman who had aborted five months previously.

I propose to describe the microscopic appearances presented by this specimen under two headings: (1) The Fœtal Remains and the Changes in the Muscular Wall adjacent to these; (2) The Changes in the Mucous Membrane at a Distance from the Placental Villi.

The Fœtal Remains and the Adjacent Muscular Tissue

The *placental remnants* consist of a number of villi embedded in the blood clot. The ectodermic and the mesenchyme cells are in some places well preserved and in other places markedly degenerated. For the most part the villi do not come into direct contact with the uterine tissue. Here and there, however, they lie up against this, and in one or two places they may actually be seen situated in a vessel.

The *maternal tissues.* In the proximity of the villi the mucous membrane has almost entirely disappeared. Here and there a gland or two surrounded by the stroma cells may be seen. These are usually

enlarged in a decidual manner. These regions correspond to the incursions of the mucosa into the muscular tissue. The muscular tissue immediately bordering on the blood clot is in a state of coagulation necrosis, exactly as described in the wall of the pregnant tube. As in the latter site, it is richly sprinkled with red blood cells. Immediately subjacent to this the tissues are infiltrated with leucocytes, chiefly of the polymorphonuclear type. Even at a distance from the villi the muscular tissue is degenerating. In these respects the changes coincide with what I have already described in connection with the pregnant tube.

The *changes in the vessels* correspond to those observed in the pregnant tube. As I have discussed these in full in the last section, it will be necessary to refer to them here only in brief. In all the sections there is a hæmorrhagic escape from a large number of the vessels, even at a distance from the region of the villi. In the marginal area the blood is passing directly into what corresponds to the intervillous space through the gaping mouths of the opened-up vessels, or it is seen traversing the maternal tissue intervening between the vessels in the neighbourhood of the fœtal remains and the main blood space. The fact that these changes are widespread, whereas at no spot is there visible any direct invasion of the uterine wall by the chorionic cells, proves beyond doubt that the blood escape is not due to a fœtal infiltration and destruction of the vessel walls. As before the alterations in the vessel walls demonstrate convincingly that the process is due to tissue changes that determine an active imbibition of the blood fluid and later of the blood corpuscles. Evidence of this is seen in the changes in the intimal and connective-tissue cells, to which attention has been drawn. The stages in the process are just as easy to follow as in the pregnant tube (Figs. 43, 44). The exodus of the red cells into the surrounding tissues is present both from the vessels coursing through the necrosed regions and from those whose walls are well preserved. On the whole it is more evident in the former, and this doubtless because of the greater intensity of the tissue changes.

As in the pregnant tube it is found that a decidual formation in the tissue cells prevents the irregular blood escape.

In many places, especially in the proximity of the villi, there is a marked distension of the vessels. In some instances this has resulted in the formation of sinus-like expansions such as I have described in the wall of the pregnant tube. In these cases the wall is formed by a

layer of flattened cells only. As before there is often an irregularity and unevenness of the bounding walls. In other cases the increase in diameter has involved the vessels coursing through the degenerating tissue in the neighbourhood of the villous remains. The confines may be regular, but they are often ragged and uneven, and it looks as if the expansion were due to a gradual solution of the necrosed tissue by the blood fluid. Round the periphery of these spaces the red corpuscles are usually seen streaming into the adjacent tissues through the wall, in a manner similar to that present in the wall of the pregnant tube. As already mentioned, where these blood tracks approach the intervillous space the red cells which escape through their walls are often seen passing across the maternal tissue partition intervening between the two blood regions.

Changes in the Uterine Mucous Membrane at a Distance from the Fœtal Remains

Round the uterine cavity the mucous membrane is well retained. To the naked eye it is seen to be deeply congested. In this section I wish to refer to important microscopic changes which it exhibits. For purposes of description I have chosen a region of the mucosa at the pole of the uterine wall opposite to that to which the blood clot and villi are adherent. In the sections no fœtal cells are present, and the changes are therefore not dependent on a direct invasion by the chorionic elements.

In many places there has been a loss of the superficial epithelium, and in some places the surface layers of the stroma with the gland orifices are wanting. Apart from this the glands are normal in appearance. In the *vessels and the interglandular connective tissue* there are changes of importance from the point of view of one of the objects of this research. In most places there is present a well-marked hæmorrhagic escape. This has involved the upper two-thirds of the mucosa; the lower third has almost invariably escaped. The bleeding has led to a ploughing up of the stroma, the cellular elements of which are often widely separated from one another. For the most part the extravasation is greatest in the surface regions. The mode of the blood escape from the vessels is often easy to trace. In the better supported vessels the stroma cells are becoming stripped off, often in concentric layers from without inwards. When this has occurred to the extent of leaving only the intimal cells, or even before, the red

cells are liberated and are seen to be streaming in quantity through the wall into the surrounding tissues. There is often present a wholesale opening out and displacement of intima as well as surrounding stroma by the escaping blood. This results in an expansion of the vessel, and then it is usually impossible to distinguish original intimal from original supporting cell (Fig. 45).

We thus see that in many respects *the changes exhibited by the mucous membrane in this specimen coincide with the changes which I have described in connection with menstruation.* The vascular and surrounding stroma alterations are identical in nature with those previously recorded. The only difference is one of degree—in this case the bleeding is greater than is found in normal menstruation. This factor probably accounts for the separation of the surface epithelium and stroma which has occurred in places, though, of course, it is possible that this is an artefact.

How are we to account for these remarkable changes which, so far as I know, have never before been noted in this condition? The hæmorrhage present is clearly not due to an opening up of the maternal vessels by a direct invasion of the chorionic cells; on the other hand it would seem likely that they must be dependent on the presence of the fœtal elements. It seems to me that the hæmorrhagic escape must be determined by the same factor which, in the muscular wall of the uterus underlying the villous fragments in this specimen, and in the wall of the pregnant tube, results in an irregular and sometimes excessive bleeding from the vessels, even at a long distance from the actual locality of the fœtal cells. We have seen that in the wall of the pregnant tube the condition is probably due to the liberation of some substance of a chemical nature which, while acting most vigorously in the immediate proximity of the fœtal cells, gradually extends the sphere of its activity to a remote distance. The excessive extravasation exhibited by the mucosa in this specimen is in all probability due to the well-demonstrated susceptibility of the stroma tissue and vessels. This I have referred to in detail in a preceding section, and I have there shown that the structural peculiarities of the stroma protoplasm enable it to respond with the greatest advantage to the influence which determines the menstrual changes. The chorionic substance in this instance probably reaches the mucosa directly. It is clear that the surface of the mucosa will be continually bathed by any material in solution escaping from the villi. This explanation of the phenomena seems to me the more rational one, though, of course, it is impossible to

say with certainty that the chorionic influence is not transmitted to the mucous membrane through the medium of the blood-stream.

A fact of considerable clinical importance is revealed by the study of this specimen. *The severe bleeding from which the patient had suffered was derived not only from the vessels in the immediate proximity of the villous remains but also from the mucous membrane at a considerable distance.* The appearances warrant the conclusion that a large amount of the blood escape was derived from this source. The conditions present here correspond in many details to those seen in the pregnant tube, where there is apt to be a free blood escape from the vessels at a remote distance from the chorionic cells. This is especially true of the finer vessels. In several of my specimens there had obviously been a continual oozing from the small vessels towards the peritoneal aspect of the tube.

Summary

(1) In the case of retained placental fragments the vascular changes coincide with those seen in the pregnant tube. The vessel walls open up in response to the tissue changes induced by the substance derived from the chorionic cells. The œdematous and blood escape are often present at a long distance from the villi.

(2) In the mucous membrane, at a distance from the villi, there are present stroma and vascular changes similar in nature to those normally found during menstruation.

(3) The bleeding from which the patient suffered was derived in part (and probably largely) from the mucosa at a distance from the villous remains.

MATERNAL TISSUE CHANGES IN CHORIONEPITHELIOMA

The material consists of four uteri, which were the seat of a well-marked chorionepitheliomatous infiltration. Three of the specimens were removed by vaginal hysterectomy, and were immediately transferred to the hardening fluid; the fourth case, which includes sections from the lungs in which there had occurred metastatic deposits, was obtained post-mortem. In all the cases the preservation, as judged by the condition of the fœtal elements, is good.

The investigations recorded in the following pages were carried out with the idea that a study of the changes induced in the uterine wall

by the malignant invasion of the cells of the fœtal ectoderm might shed still further light on the manner in which the ovum establishes its intimate relationship with the maternal tissues in the case of a uterine pregnancy.

In the last chapter we have acquired evidence which tends to prove that the orthodox conception of the exact manner in which the fœtus is furnished with its supply of maternal blood must be completely modified in the case of a tubal pregnancy. In that condition, which corresponds to a fœtal invasion of the maternal tissues of a benign nature, we have seen that in response to the presence of the chorionic elements there are set into action complex changes in the maternal tissues which result in their actively imbibing the blood fluid and cells, and, in the case of the vessels in the immediate proximity of the fœtal ectoderm, culminate in a wholesale escape of the red blood corpuscles across the space intervening between the vessel lumen and the villous line of advance.

In the case of chorionepithelioma we are dealing with a tumour growth composed of masses of fœtal cells which actively invade the wall of the uterus. After a large amount of discussion (it is doubtful whether any tumour has ever given rise to so much dispute as to its origin) this growth has now been definitely proved to owe its origin to a malignant over-growth of the epithelial elements of the chorionic membrane. Hence the name. The indisputable demonstration of its true nature we owe, in the main, to the researches of Marchand on the Continent and to Teacher in this country.

Primâ facie it would seem likely that the manner in which this tumour is provided with its supply of maternal blood would correspond to the manner in which the ovum engrafted in the uterine mucosa opens up the maternal vessels, for this is accomplished, as we know, by the activity of its epithelial covering. In either case the object of the tissue changes induced is the acquisition of a plentiful supply of mother's blood. In either case we are dealing with structures which are, in the main, to be considered as parasites deriving their sustenance from the maternal blood.

Chorionepithelioma, then, may be defined as an over-growth of the cells of the fœtal ectoderm, which, for some reason or other which we still imperfectly understand, has during or after a pregnancy assumed a malignant tendency. This is manifested by an infiltration and destruction of the tissues of the uterine wall, sometimes to the extent of burrowing right through to the peritoneal surface. As is well known,

this hyperplasia of the chorionic cells is very apt to ensue subsequent to the development of a hydatidiform degeneration of the fœtal villi. On section the uterine wall is seen to be studded with clumps of the fœtal cells, which often appear to be cut off from one another and lie as islets embedded in the uterine wall. It is usually easy to recognise in these masses both of the cellular elements of the fœtal chorion, the rounded or polygonal cells, with large nuclei, corresponding to the Langhans' cells of the ectoderm and the plasmodial multi-nucleated masses, which correspond to the syncytial covering of the fœtal surface. The main changes in the maternal structures are seen in the production of a widespread œdema and blood extravasation, the latter being especially marked round the masses of the fœtal cells. In addition there is induced a progressive degeneration of the muscle of the uterus. The fibres swell up, the nuclei become large and pale. This is followed by a disappearance of the outlines of the fibres, which often coalesce to form a homogeneous structureless mass devoid of nuclei. In later stages of the degeneration the muscle elements disappear altogether, apparently entering into a state of solution.

One of the most characteristic features of this tumour growth is the excessive hæmorrhage which its presence provokes. In the literature the mechanism of this is supposed to depend on an infiltration or corrosion of the vascular walls by the chorionic cells, which give way, releasing the contained blood, which is extravasated by the force of the blood-stream, and thus furnishes the nutriment of the growing cells of the tumour. The orthodox conception of the process is thus expressed by Teacher in his admirable monograph:—"The advancing tumour attacks the vessel from without, destroying and replacing the wall. . . . When it reaches the endothelium the tumour cells tend to spread along just under it for some distance, so that the vessel may come to have the appearance of a tube of endothelium in a sheath of large tumour cells. . . . Sometimes a plug of tumour regularly invaginates the endothelium into the lumen." The hæmorrhage is caused by the fact that "finally the endothelium disappears or gives way. When this occurs, on the one hand the tumour cells enter the vessels and on the other extravasations of blood into the tumour take place." According to this description of the changes, which so far as I can discover embodies the conception universally accepted, we note that for an escape of the contained blood there must be a local destruction of the vessel wall by the infiltrating tumour cells. This once accomplished, we have a mechanical exodus of the liberated blood. Teacher in another paragraph states

that "the tumour grows into the mouths of the uterine sinuses, attaches itself, and invades them from within." According to these descriptions of the process, then, the fœtal cells are bathed in the maternal blood by one of two different methods: (1) they destroy the vessel wall, and in this way create a gap through which the blood is poured out; or (2) they grow into and along the vessel lumen in a manner which in some cases is similar to that in which the villi extend along the veins of the tube wall in the case of tubal pregnancy, and along the uterine veins in the case of normal pregnancy. It will be seen that these conceptions regarding the mode of action of the tumour cells in the condition we are studying coincide accurately with the almost universally accepted view of the method of action of the chorionic cells in the case of a tubal pregnancy, and, as will be noted later, also in the case of normal uterine pregnancy.

In all my specimens the blood extravasations, though most evident in the immediate proximity of the fœtal cells, are not confined to this region. Scattered irregularly throughout the maternal tissues there are numerous areas of blood escape round the vessels, and this even at a considerable distance from the site of the cellular invasion. It is also distinctly present in the lung tissues in which there has been the occurrence of metastatic deposits. In all of the specimens it was possible without the least doubt to recognise the red cells leaking from vessels in whose neighbourhood there were present no cells in the least resembling those of the chorionic membrane. These observations indicate that there must be in operation some influence determining the blood escape through the vessel walls other than the direct locally infiltrative and destructive effect of the chorionic cells. The more distant hæmorrhages, it is clear, must be provoked in some way or other by the presence of the chorionic cells. The fact that the blood exit through the vascular walls becomes, on the whole, more and more marked the nearer the tumour masses are reached would indicate that this chorionic influence, whilst naturally exercising its most potent action on the nearest maternal structures, spreads directly through the tissues, becoming less and less powerful until ultimately it is insignificant or becomes lost altogether. The probable nature of this influence I shall discuss later; in the meantime I shall be content to refer to it exclusively from the aspect of the structural changes which it induces in the maternal tissues.

In Plate X. is shown a fine vessel through the wall of which there is seen a passage of the red cells into the neighbouring tissues. The boundaries of the vessel are unimpaired round its entire circumfer-

ence; in other words, there is no trace of the destructive process such as is demanded by the orthodox conception cited above. At a small distance there are seen the chorionic cells, but between these and the vessel wall there is a distinct interval devoid of the fœtal elements. The fact that one can detect with ease the passage of the individual cells through the vessel wall disproves with certainty what otherwise might have been urged, namely that the hæmorrhage in these cases is derived from the same or another vessel whose wall had been invaded in an adjoining part of the uterine wall. I maintain that these appearances, which are found with ease in all my sections, demonstrate that there is in existence some process different from that advanced by previous investigators on the subject. We see also that by this influence the fœtal elements are brought into contact with the maternal blood. It will be noted that, so far, these investigations coincide with those which I recorded in connection with the blood escape in the pregnant tube and in the condition where placental fragments are retained *in utero.*

As the result of these observations we are compelled to amplify the conception entertained by Teacher and others. If both views be correct, then we have to deal, in regard to the manner in which the tumour masses acquire their nutriment in the shape of the maternal blood, with two separate and distinct processes. We have in the first place a local destruction of the vessel walls by the direct chorionic infiltration, with a subsequent mechanical outpouring of the blood over the fœtal masses, and we have in the second place some tissue or vascular alterations which are independent of an actual chorionic invasion. I shall advance evidence in a later part of this investigation which tends to indicate that the important factor is not the local breach created in the vessel wall, but that this process is probably to be looked upon rather as an incident in the advance of the tumour cells than as the cause of the blood escape.

In the meantime I shall pass on to consider the possible factors responsible for the escape of the red cells from the vessel lumen where a direct invasion by the fœtal cells can easily be put out of court.

Cause of the Blood Escape from the Maternal Vessels

The process may be divided into two more or less distinct stages. In the first place we have a dropsical opening out of the tissues; this is followed by the hæmorrhagic escape from the vessels. We have

already noted that an œdematous infiltration of the uterine wall is one of the most characteristic changes induced by the presence of the chorionepitheliomatous masses. It is wide spread, and reaches its maximum in the immediate proximity of the chorionic cells. By its means there is produced a spreading apart of the muscle bundles and a teasing asunder of the individual muscle fibres. The process is most evident, for the most part, in the environment of the vessels, and can be seen leading to an opening out of the structures forming the vessel walls. In many places it is easy to detect œdematous tracks ploughing their way through the vessel walls into the neighbouring region, where they usually expand into wider spaces, because of the easier separation of the tissue elements. Sometimes in the better supported vessels this condition is limited to the vessel wall, but as soon as it involves its entire thickness, and frequently before, the neighbouring tissues are involved in the process. Along the tracks thus created it is in many places possible to discover the escape of the red cells; in fact, the dropsical infiltration is such a constant precursor of the corpuscular escape that, as in the case of the pregnant tube, it must be looked upon as a preparation for the exodus of the more solid elements of the blood.

If we examine the vessels in the uterine wall we observe, in many places, and even at a considerable distance from the chorionic cells, the appearances represented on Figs. 46-50, Plates X.-XII. In the vessels represented there is seen a swelling and bulging towards the vessel lumen of the endothelial layer of cells. Sometimes this is indicated by a fluid distension involving the individual cells (Figs. 46, 47, Plates X., XI., XII.); in other cases it is represented by a dropsical accumulation in the immediately subendothelial space, which has resulted in a wholesale floating up of a sheet formed by several of the cells (Fig. 48). The fluid expansion of the isolated cells, which project into the lumen like a row of beads set into the vessel wall, is a constant precursor of the more marked accumulation. It is obvious that these appearances can be due to one cause, and one cause only, namely, some alteration in the cell protoplasm which has determined an absorption or imbibition of fluid from the vessel lumen. When the cellular distension reaches a certain degree there occurs a separation of the confining layer of cell substance. Whether or not this is dependent entirely on mechanical causes I am unable to state with certainty. It seems to me, however, not unlikely that the cytoplasmic changes, which have culminated in the opening up

of the cell substance by the fluid imbibed, may of themselves determine the softening and ultimate giving way or solution of the remaining portion of the cell substance which has been displaced to the periphery. In some places it would seem to take place, in the first instance, on the aspect towards the vessel lumen (Fig. 50); in other cases there occurs a disappearance of the films intervening between the adjacent endothelial cells, with a consequent amalgamation of the contiguous cell spaces; in other instances the first rupture occurs on the outer aspect. The accumulation under the endothelium, it is clear, must be, for the most part, extracellular in position, and, as it results in a projection of the endothelial sheet towards the vessel lumen, the contained fluid must have collected under a hydrostatic pressure in excess of that exerted by the lateral blood tension. Here, again, the accumulation must be due to a diffusion of fluid across the endothelial film (which has functioned as a colloidal membrane) from the blood-vessel lumen, which is a region of lower, to the tissue space, which is a region of higher, "osmotic" tension. We thus see that the process, which led to a fluid distension *inside* the cells, has resulted in a dropsical accumulation *outside* the cells. It can only be explained as due to the presence in the tissue spaces of crystalloidal elements which have been set free in consequence of the activity of the chorionic cells.

So far, then, we have no difficulty in understanding how the innermost portion of the vessel walls becomes opened out, and how to this extent there may be a liberation of the blood contained in the vessels. How is the teasing asunder of the tissue elements, and, in the case of vessels other than the very finest, of the outer portion of the wall to be explained? If we satisfactorily explain these phenomena, we have little difficulty in determining the rationale of the escape of the red blood corpuscles into the surrounding tissues. From the fact that their structure results in a forcing into prominence of the successive steps of the process, I shall still confine my remarks to the thicker-walled blood-vessels. The next stage is seen in an opening of the vessel boundary in the region immediately external to that already referred to. Here again it is easy to determine that there must still be in operation the same "osmotic" influences. These fluid tracks are represented often by a sort of honey-combing of the muscular tissue of the vascular wall (Plates X., XII., and Figs. 47, 48); in this, the earliest stage of the process, there are still present bridging processes of the degenerating protoplasm which interrupt the completeness of the tracks. In

some cases on section this appearance is evidenced by the presence in the wall of a large number of spaces varying from a size just recognisable with the highest powers of the microscope to comparatively large vacuoles; in other cases there is created a complete or an almost complete track in the vessel wall leading into the perivascular tissues (Fig. 47). Such a track may communicate directly with the vessel lumen when there has been a disappearance of the lining cells. In other cases the endothelium may still persist, and it is often seen to be bulged towards the vessel cavity.

The process of fluid imbibition is, as already stated, exhibited by the endothelial cells in a manner which is almost diagrammatic in its clearness. In them we have demonstrated with precision the mechanism which, I believe, dominates the whole process of the œdematous escape from the vessel lumen across the vessel walls into the surrounding tissues, and which in the finer vessels is readily followed by an exodus of the blood corpuscles. In the description of the changes in the vessels of the pregnant tube, which, it will be noted, are identical with those at present under discussion, I have already pointed out that we are furnished with confirmatory evidence of the truth of this interpretation of the phenomena in the changes which are seen in the connective-tissue cells. These were seen to exhibit the process of fluid imbibition in a manner similar in every respect to that occurring in connection with the endothelial cells. In the uterine wall, in the case of chorion-epithelioma, it is likewise easy to find that the intracellular fluid accumulations are not confined to the endothelial layer. It is often present in the connective-tissue cells in the vessel wall. The same change is detected in the outlying connective-tissue cells (Fig. 52). As described in the wall of the pregnant tube, in two adjacent connective-tissue cells the intracellular spaces filled with the imbibed fluid may flow together, leading to the production of a correspondingly large cavity bounded by the remains of the two cells. By the inclusion of a third cell in the process we obtain a space bordered by three cells, and so the process may extend till ultimately we have large œdematous spaces.

The description of the changes in the thicker vessels applies with equal force to the fine vessels. Here, as can easily be understood, the œdematous ploughing up of the adjoining tissues is, on the whole, much more evident, and there is more apt to be a leakage of the corpuscular elements of the blood. In the fine capillary vessels the stages of the process are often more difficult to follow. This is dependent on the

fact that, with the onset of the endothelial and tissue changes, there is permitted an early and an easy exudation of the fluid, which escapes leaving little trace of the steps of the process behind it. That the same process is, nevertheless, in operation here also, I have been repeatedly able to determine by the discovery in the early stages of the same fluid swelling of the cells of the endothelial layer. The giving way of the fine cell films in such a case at once creates a direct communication between vessel lumen and tissue space, and thus determines the possibility of an easy mode of escape for the blood corpuscles.

It was noted in connection with the changes exhibited by the wall of the pregnant tube that the muscular tissue undergoes a progressive disintegration especially in the neighbourhood of the fœtal elements, until it ultimately becomes represented by a homogeneous, faintly staining mass, in which all resemblance to the original muscle fibres is lost. The connective-tissue cells, on the other hand, resist the process to a marked degree, and, even in the immediate proximity of the ovum, they may be recognised with well-preserved nuclei. In most places they were found to be enlarged, both in nucleus and cell body, and often in a way which identified them with the decidual cells of the uterine mucosa in the case of an ordinary pregnancy. Exactly the same description applies to the connective-tissue cell of the muscular wall of the uterus in chorionepithelioma (Fig. 53).

Changes in the Muscle

The investigations which I have just recorded demonstrate that the transmission of the fluid from blood-vessel to tissue is dependent on protoplasmic changes which are set in action by the presence of the chorionic elements. The part played by the endothelium and the connective-tissue cells in the process is easily demonstrable. That the remaining elements composing the uterine wall, namely the muscle, contribute their share to the process can hardly be doubted. It has been seen that, especially in the proximity of the tumour cells, there is present a marked degenerative change in the muscle fibres. They swell up, their contour becomes obscure, the nuclei disintegrate, and there is produced a homogeneous, structureless material. There is present, especially in the neighbourhood of the fœtal cells, a gradual thinning out and disappearance of this fibrinous mass. That the removal of the muscle fragments is due to a direct absorption or phagocytosis on the part of the chorionic cells is unlikely. In none of my sections is there any evidence of this process. In this respect my specimens entirely

coincide with those of Teacher. The fact, moreover, that the softening and disappearance of the remnants of the muscular tissue is found at a considerable distance from the tumour cells would tend to indicate that some other process must be advanced to explain the phenomena. It seems certain that there has been induced by the chorionic activity a change in the muscle fibres which culminates in a breaking up of their substance and a subsequent solution of the products of disintegration. The fact that I have frequently been able to detect in my specimens changes in the muscle fibres which coincide in every respect with those exhibited by the endothelial and the connective-tissue elements would indicate that with the progressive degeneration to which they are subject we have associated chemical protoplasmic changes of the same order. In Plate XIII. is represented a condition exhibited by the muscle fibres. There has taken place an absorption of fluid which has accumulated in definite vacuoles in the cell substance, and has displaced this in an outward direction. Here again we have obviously the same phenomena in evidence, phenomena which are amenable to one explanation and one only, namely that in association with the muscle changes there has occurred a liberation of "crystalloidal" elements, with a consequent diffusion into the interior of the fibre. These changes are again exhibited in all degrees. With them, however, as we have indicated, there is apt to be a speedy disappearance of the muscle substance, which seems to pass into solution with great readiness. This fact, in all probability, explains why the actual process in operation is apt to be quickly obscured. The various stages of the changes in the muscle elements are well shown in Plate XIII.

Recent research on experimental lines would seem to indicate that the chorionic structures are provided with an enzyme or enzymes which have the faculty of digesting musele, etc., and of transforming their protein constituents into substances crystalloidal in nature. If this evidence be trustworthy we are supplied with information in favour of the conceptions I have advanced above (Chapter VI.).

Our histological investigations, then, have furnished us with evidence which points to the fact that in response to the influence of the fœtal cells there have occurred widespread chemical alterations in the cells which are accompanied with an elevation in their intracellular affinity for fluid. *These changes, we have now been able to discover, are exhibited by all of the three important cellular elements of the uterine wall, namely, the endothelium, the connective tissue, and the muscle cells.* The fluid escape which these changes induce is some-

times easily traced by stages from the innermost portion of the vessel wall through the outer part and ultimately into the tissues. In some cases, however, the immediate environment of a vessel which has resisted the teasing out of the wall thus caused is found to be the seat of a well-marked œdematous infiltration. In such a case we are, I think, justified in thinking that the colloidal membrane essential to the process has been formed by the entire thickness of the wall, which in these instances is usually especially compact. In the other condition, where the fluid has gradually leaked through the wall, leaving its track behind it, the colloidal membranes have been formed by the successive parts of the vascular wall. These are apt in the process to give way. When such occurs we have the production of a breach in the wall, through which the corpuscular elements may escape. In Fig. 48 is shown the earliest stage of the process. Here the blood has passed into the vessel wall and has accumulated under the uplifted endothelial sheet. Though there is no gap visible in this figure, it would seem likely that for the passage of the corpuscles from one region to another a complete breach is essential. The next stage of the process is indicated on Plate XII. Here the fluid infiltration has resulted in a teasing apart of the walls to the extent of permitting an escape of the red cells into the media. In some instances the red cells may be followed a stage further, *i.e.* through the vessel wall into the adjoining tissues. This is especially evident in the proximity of the fœtal elements, and on the whole, except here, is a condition of rarity in vessels of any thickness. Throughout the uterine wall there is, even at a distance from the tumour cells, a more marked hæmorrhagic escape from the finer vessels (Plates X. and XI.).

How is the escape of the red cells actually accomplished? Is it due solely to the fact that the breaches created in the vessel walls have permitted a mechanical extrusion of the red corpuscles, or is it the case that the sucking or imbibing of the fluid from the vessel lumen is associated with a continual stream from the vessel, which, after the breaking down of the tissue barriers, at last drags out the blood cells? Whether we have to deal with the former process, namely, the *vis a tergo*, or the latter, the *vis a fronte*, it is impossible to assert with precision. From what we have observed, however, it seems not unlikely that the latter must play an important part. It, moreover, explains how the immediate surfaces of the chorionic masses are often bathed in maternal blood. The tissue changes are more and more marked as we approach the fœtal cells, and reach their maximum in the immediate proximity of these elements. This would imply that there is produced

a gradient of "osmotic" tension rising, probably rapidly, to the chorionic surface. This would result in a streaming of the fluid and corpuscles towards the chorionic surface from the vessels in this region.

It would seem not unlikely that an additional factor tending to lead to an attraction of the blood to the chorionic surface is to be found in the fact that the fœtal cells must be actively imbibing the tissue fluid in their immediate proximity. This would result in a keeping up of the flow from behind, and an ultimate flushing of the surface with red cells whose numbers would tend to increase as more and more of the fluid was hurried forward to supply the wants of the chorionic cells. The evidence which we have in the shape of a structural adaptation of the chorionic surface for such a process of active imbibition will be touched on in a subsequent section of this book.

Is a Direct Infiltration of the Vessel Walls by the Chorionic Cells the Cause of the Blood Escape?

I have in several places referred to the fact that according to Teacher and others, the tumour masses in the case of chorionepithelioma are furnished with their supply of maternal blood only after they have invaded and opened up the uterine vessels. The destruction of the vascular wall is followed by a mechanical escape of the contained blood which then flows over the surface of the fœtal masses. The bathing of the fœtal cells by maternal blood is also, according to these observers, determined to a smaller extent by the fact that after working their way through the vessel walls the tumour cells may spread along within the vessel lumina, either lying free or attached to the inner aspect of the wall.

With regard to the occurrence of this latter process I am in entire accord with the above-mentioned observers; I have often noted it in my sections. I am inclined to believe, however, that from the point of view of affording an explanation of the manner in which the chorionic cells come into contact with the maternal blood it occupies a position similar to the process by which the surface of the villi, which bore their way into, and spread along, the maternal vessels (probably veins) in the uterus in ordinary pregnancy, and in the pregnant tube, come to be bathed in the maternal blood. In other words it must be considered to play a part of comparative unimportance; only the regions of the chorionic masses projecting into the vessels can be supplied with their nourishing fluid. Is this other mechanism to be sought for in the fact that the breaches created by the chorionic cells in the walls of the

vessels permit a wholesale escape of the contained blood by virtue of the intravascular pressure?

The conclusions which I have come to on this subject are best summarised by repeating what I have several times stated, namely that the extension of the chorionic elements through and into the vessels is to be considered not as a feature of the process which is essential to the growth of the tumour masses, but rather merely as an incident in the invasion of the uterine wall by the fœtal cells.

In many places the tumour cells are found to have replaced the tissues forming the vessel wall, and are seen to project, usually by a fairly extensive surface, into the vessel lumen. In other places one can see the fœtal cells approaching the vessel but still separated by a portion of the uterine wall from the lumen. Across this intervening septum it is often possible to detect the streaming of the red cells towards the tumour elements, and this even when the vessel confines are still apparently intact, or at any rate certainly before any of the chorionic cells have extended as far as them (Plate X.).

At the same time the maternal tissues are usually spread apart by an œdematous infiltrate. These observations, which I have been able to make in all my sections with the utmost certainty, prove beyond doubt, as already stated, that for an exodus of the fluid and corpuscles a direct infiltration and destruction of the vascular walls is not essential.

Besides the vascular changes associated with an increased fluid and corpuscular escape, there are other alterations of considerable interest and importance. These fall into two classes. In the first place, scattered throughout the uterine wall there has occurred the formation of large sinus-like expansions of the fine-walled vessels; in the second place there is found in some places the formation of new capillary vessels. We thus note that in this respect the changes in the thin vessels coincide with those which I have described in connection with the wall of the pregnant tube. The actual mode of production of these sinuses and new vessel branchings, also, would seem to conform with that which I have recorded in connection with the pregnant tube. My specimens of chorionepithelioma, unfortunately, do not permit of such a perfect study of the cellular changes responsible for these vessel alterations, which, we shall remember, were demonstrated in some of my sections of the pregnant tube in a manner which was almost diagrammatic in its clearness. In some places, however, we have the successive steps in the two processes exhibited in a way which leaves little room for uncertainty.

Mode of Expansion of Vessels—with and without Tumour Masses

In this section I wish to refer, in the first place, to the sinus-like vessel expansions which are scattered about the uterine wall. Their boundaries are formed by a layer of flattened cells. In size they exhibit great variation. Some are comparatively small, whilst others have in their formation extended through a large territory of the uterine wall. They vary greatly in shape. In some places they possess a uniformly circular or oval contour; for the most part, however, they have irregular boundaries. In many cases their outlines are extremely uneven, and the shapes assumed would seem to be determined to a large extent by mechanical influences. Thus they are often seen to skirt muscle bundles or to insinuate their way between two muscle masses. In this way there are often produced marked differences in their diameter at different parts of their course. Where there has been an obstacle to their expansion they have remained narrow, sometimes with a width not more than that of a fine capillary. Beyond the mechanical obstruction they again expand, only, perhaps, to become attenuated at a further part of their course (Figs. 54, 55, 56). For the most part their number and size are greater the nearer the chorionic elements are approached. It will thus be seen that in their characteristics they closely resemble similar structures which I have described in the wall of the pregnant tube. They likewise correspond closely to the sinus-like expansions which are found in the uterus during an ordinary pregnancy.

The way in which the expansion of the wall of such a space is brought about is sometimes clearly discovered by a close study of the cellular changes in the endothelial lining and the immediately apposed connective-tissue cells. Where a vacuolated connective-tissue cell lies against a vacuolated endothelial cell there is apt to be an amalgamation of the cell spaces. The exact manner in which the fusion of the two cell spaces occurs it is difficult to say. Is it due to a disappearance of the cell membranes intervening between the fluid spaces of two entirely distinct and independent cells, or is it not rather merely due to a passage along and expansion of the protoplasmic communications which we can often detect passing between the endothelial and the connective-tissue cells? By means of this process there is rendered possible a gradual extension of the boundaries of the sinus till it may reach the proportions we have indicated. If the change occurs uniformly all round the

circumference of the blood space there is a symmetrical and equal increase in the diameter. If, however, a muscular bundle or some other obstacle is interposed in its path of advance, the increase in that part becomes impeded with the result already noted. In many places one is able to detect a gradual opening up of the vessel walls and advance of the blood cavity thus produced through the maternal tissues to meet the chorionic masses (*cf.* pregnant tube).

It is often possible to detect the same expansion occurring in the walls of a vessel into and along which a mass of the tumour cells have grown. As we have already noted, this is a condition usually not difficult to find in a section of the uterine wall which is the seat of a chorionepitheliomatous invasion. The same changes are detected where an embolus of the tumour cells has lodged within a maternal vessel. As has been pointed out by Teacher, in such a case there is apt to be a gradual expansion of the vessel, which may attain a diameter greatly in excess of that of the contained tumour mass. In this change Teacher sees an analogy to what occurs in the pregnant uterus, where, as is well known, there is a gradual recession of uterine mucosa before the fœtal elements. This provision, which is essential to the formation of the intervillous blood space, results in the production of a gestation cavity in size greatly in excess of the dimensions of the contained ovum. I have referred to the same change in the wall of the pregnant tube. In the account of the changes which were present in the uterine mucous membrane in the case of their early embryo, Bryce and Teacher somewhat amplify the original observations of the latter writer. In page 42 of that publication they make the following statement:—" We may here digress for a moment to point out a very suggestive analogy with the normal ovum in respect of its influence on adjacent maternal tissues, presented by an embolus of *chorionepithelioma* in its development into a secondary tumour. The embolus, usually somewhat larger than the embedded ovum, lodges in the fork of a blood-vessel, the wall of which soon shows degenerative changes identical in character with those seen in the decidua around the present ovum. These occur prior to the invasion of the tissues by the tumour cells. The injured blood-vessel dilates into a more or less globular aneurismal cavity, and there may be considerable growth of the embolus in its interior before invasion begins. The blood in the neighbourhood of the embolus does not coagulate until secondary changes, which need not be discussed here, bring about that result. After a time the tumour elements invade the maternal tissues, and the embolus becomes attached. At this stage appearances may

be found very similar to those around the margin of Peter's ovum."

In his description of this process Teacher has confined his attention to those vessels in whose walls there is present a marked degenerative change. In many of my sections I have been able to note an aneurismal expansion of vessels containing a clump of the fœtal cells, in which the walls are formed by a complete layer of flattened cells. In some places this expansion of the vessels has occurred to an extreme degree, and apparently in response to the activity of a comparatively small clump of the tumour cells (Figs. 54, 55). Such a blood space corresponds in every respect to the sinuses which we have seen to be scattered through the muscular wall of the uterus. These, I have pointed out, are formed, not by a gradual mechanical giving way of degenerative tissues, but by a process in which "active" changes in the endothelial and connective-tissue cells are seen to take a prominent part. These changes, which must be dependent in some way on the chorionic influence, result in a gradual invasion of the surrounding tissues by the expanding blood cavity, and are associated with an incorporating within its walls of the altered connective-tissue elements. This process of vascular expansion is dependent on the intracellular changes which are responsible for many of the phenomena associated with the presence of the fœtal elements. These so alter the chemical composition of the cell substance as to determine an imbibition of fluid by the cell body. In many cases this process culminates, especially in the case of the degenerating muscle, in which the same changes are visible, in a wholesale transformation of the cell substance into materials which pass into solution in the imbibed fluid.

Does the aneurismal expansion of the vessels, to which we have referred, demand the introduction of a process different from that just mentioned and which, I have shown, suffices to explain the sinus-like vascular distension in other places? As the results are similar in every respect, with the exception of the fact that in the vessel with the embolus or tumour extension the immediate proximity of the chorionic elements has resulted in a greater degree of expansion, it would seem probable that in each case we are dealing with exactly the same phenomena. That this is actually the case I have been convinced by a study of the changes in the endothelial and adjacent connective-tissue cells round the margin of such an expanding vessel. One can often detect the results of the same changes to which I have repeatedly called attention (Plate XI., lower part).

In most places where the maternal tissues have receded from the chorionic cells the degenerative softening changes have obscured, often quite beyond recognition, the actual steps of the process. Here again, however, we can sometimes detect, through the veil cast over the changes by the disintegration present, exactly the same process in operation. In all the various types of vessel involved in the process of progressive expansion in consequence of the chorionic activity it is possible in many places to distinguish the fact that we have in operation factors other than those suggested by Teacher. Again we can determine the existence of a direct fluid imbibition by the tissues. We see a swelling up of the endothelial and connective-tissue cells, and often also of the muscle fibres by fluid derived from the adjacent blood lumen (Fig. 51, Plate XI.). In fact we can often discover with certainty that, as before, the opening up of the tissues by the fluid is determined by changes in the tissue elements, changes, moreover, which result in a teasing asunder or opening out of the vessel boundaries by a force greater, and probably much greater, than that of the intravascular pressure. After a separation of the inner portion of the wall occurs, the constitutent elements are so opened out that in this region we lose sight of the process completely. It can now, however, often be seen advancing in the same way into the more external structures. These, in their turn, become opened out and displaced in the same manner, till ultimately we may have produced a blood space vastly greater than that originally present. That this may occur is demonstrated by finding the blood channel shrinking often to meagre dimensions immediately beyond the region of the tumour mass (Fig. 55). The difference between this process and that which results in a more or less uniform expansion of the vessel wall will be seen to be one more apparent than real. In each case the predominating influence is the active change in the tissue elements. In these phenomena we have exemplified a fact of considerable interest and importance, namely that the presence of the tumour elements, under some circumstances, besides leading to changes which determine a flow of the blood constituents towards their vicinity, may so act as to result in a streaming away of the fluid (and sometimes of the corpuscles) from the position which they occupy. I mention this fact because it seems to me to demonstrate in a convincing manner the important *rôle* which alterations in tissue composition play in the transference of the blood from vessel to adjoining structures.

In many cases such expansions of the tumour-containing vessels may occur in an extremely irregular manner; instead of being more or

less smooth in outline the resulting blood space may exhibit an irregular and ragged margin. This depends on the process having involved some parts of the wall more than others (Figs. 54, 55, 56).

In addition to this simple imbibition of fluid by the endothelial and connective-tissue cells, which subsequently become displaced in an outward direction, there are other changes of considerable importance, which are exhibited in such an aneurismal formation in the course of the affected vessel. Here, again, there is found a thinning out and disappearance of the tissue elements, especially involving the muscular fibres. These, as I have pointed out on a preceding page, after exhibiting alterations which point to the fact that they are the seat of katabolic changes, associated with the liberation of "crystalloidal" elements, soon undergo a progressive softening and breaking up, and ultimately disappear altogether. This can be explained only by assuming that the chorionic influence has led to a sort of digestion of the fibres, which then pass completely into solution in the imbibed fluid. The same changes are sometimes seen, though never to anything like the same degree, in the connective-tissue elements.

After this description of the vascular changes which, though varying greatly in their results, are dependent on the same fundamental cause, we are now able to understand the appearances often presented by a vessel when a clump of the chorionic cells is advancing towards its neighbourhood. I have already referred to the fact that the manner in which the fœtal elements reach the intravascular lumen is not wholly due to a simple destruction of a vessel wall, which, in the process, acts a part entirely passive in its nature. We can understand how an appearance which is frequently observed, namely, that before any of the fœtal cells actually reach the vessel the walls of this often become teased out, and especially in the case of a thin-walled vessel, may virtually advance through the tissues to meet the invading cells (Figs. 56, 57, and Plate XI.). The process underlying this remarkable phenomenon is exactly the same as that which determines the expansion both of the tumour-containing and the tumour-free vessels, and is determined by the chorionic activity which sets into action the tissue changes to which I have often referred. The giving way of the vessels in this way is often most evident on that side of the vessel which is nearest the chorionic cells, and still before there has occurred a projection of even isolated fœtal cells as far as the vessel wall. It is at first sight rather remarkable to note that the same opening out of the vascular wall has often occurred also on the more distant aspect. In

view of what I have said with regard to the vessel changes in general, we should, however, have no difficulty in understanding the rationale of this.

New Vessel Formation

In none of my specimens of chorionepithelioma have I been able to discover this process to the extent in which it was exhibited in the wall of the pregnant tube; where present, also, the steps of the process are never delineated in the convincing manner visible in the wall of the tube. The fact that I have been able to demonstrate the same endothelial and connective-tissue changes, and the fact that in its results the new vascular formation is the same as in the former site, suggests that the same protoplasmic changes may be the determining factor here also. I believe that these tissue changes explain the formation of the fine capillary vessels in the granulation tissue which is not infrequently found to be laid down in the maternal structures bordering on the fœtal elements (Plate X.). In other words, it is likely that, in this new vessel formation, we have merely a manifestation of the changes which enable the mother's tissues actively to carry blood to the fœtal masses (*cf.* Menstruation, Pregnant Tube, and Decidua Round Early Ovum).

Interdependence of the Action of the Tumour Cells and the Maternal Changes in Explaining the Malignant Invasion

The foregoing record sheds considerable light on the question of the cause of the malignant growth in this condition. In chorionepithelioma, as in other malignant tumour growths, there is a tendency to regard the proliferative activity of the cells of the neoplasm as the all-important factor. The invaded tissues play a part entirely passive; they are eaten away or eroded, or they are destroyed by the pressure exerted by the increasing tumour elements. The description which I have given above indicates clearly that this view, in the case of chorionepithelioma, is incomplete, and fails to recognise the existence of a factor, without which the malignant growth is impossible, namely, an active change in the surrounding tissue elements by which the nutritive blood fluid of the mother is hurried towards the regions of the tumour cells. This maternal reaction is determined by the extracellular material spreading from the tumour cells, and these develop in the direction from which their nutriment is flowing. In this way we are brought face to face with a remarkable circle of events.

Decidual Formation in the Uterine Wall in Chorionepithelioma

In many of my sections there is a well-marked enlargement of the connective-tissue cells of the uterine wall. This change is comparable in every respect to that seen in the typical decidual formation. I shall refer to these changes at greater length in a subsequent section of this research.

The Changes in the Maternal Tissues other than the Uterus, which are the Seat of Chorionepitheliomatous Emboli

For this investigation I have had the opportunity of studying the changes as seen in the case of the lung. These correspond for the most part to the changes which I referred to in connection with the uterine wall. They have, in addition, afforded me the chance of observing the manner in which the embolic masses of the tumour may be strangled and ultimately destroyed by the hæmorrhage which they provoke. For a description of these changes I would refer the reader to the admirable paper of Teacher already mentioned.

In the lung one is able to observe the blood exodus occurring in exactly the same manner as that described above. One has also been enabled to discover that here again sinus-like vascular expansions are produced by a process identical with that described in connection with the pregnant tube and the uterine wall in chorionepithelioma.

Summary of Vessel and Tissue Changes in Chorionepithelioma

By a study of the histological changes which are induced in the uterine wall by the chorionepitheliomatous masses we are enabled to draw the following conclusions:—

(1) The chorionic influence in some way or other determines the occurrence of protoplasmic changes in the cells, which lead to their imbibing fluid which can often be seen to have accumulated in the cell body under a hydrostatic tension clearly higher than the pressure of the intravascular blood and of the fluid in the surrounding tissue spaces. This we have seen can be explained only by assuming the occurrence of some chemical alteration in the cell substance which is associated with the liberation of elements with a greater affinity for fluid. These changes we have noted without the least possibility of doubt

in the endothelial cells and in the connective-tissue cells. In many places we have been able to detect an exactly similar process in regard to the muscular fibres. In other words, all the cellular elements of the uterine wall are conspiring to drag the fluid from the vessels.

(2) These changes are responsible for the well-marked œdematous infiltration from the vessels which is found in the uterine tissues in a case of chorionepithelioma. They, moreover, amply account for the blood escape from the vessels into the neighbouring tissues and towards the chorionic surface. This is dependent on active tissue changes which determine a sort of suction into the tissues of the maternal blood.

(3) An escape of the blood by merely mechanical means from a broken down vessel wall does not suffice to explain the manner in which the fœtal elements derive their nourishment. On the contrary, the fœtal cells are often seen growing towards the site from which the blood fluid and corpuscles are flowing. The significance of this I have touched on in connection with the pregnant tube. The many and varying vascular changes which are seen are dependent on the same common factor, namely the above-noted tissue changes which the fœtal cells provoke. They explain the gradual expansion of the vessels both into endothelium-lined sinuses and into irregular and ragged spaces. Both conditions may occur with or without the presence of the tumour cells in the vessel lumen. Where the wall is uneven and disintegrating this merely indicates that the muscular (or sometimes the connective-tissue elements) are succumbing to the influence causing the protoplasmic changes. Even here the expansion is probably due chiefly to an active fluid imbibition with a subsequent tissue displacement or solution.

CHAPTER V

DESCRIPTION OF VERY EARLY HUMAN OVUM—EXPLANATION OF THE UTERINE CHANGES IN PREGNANCY

Site of Ovum Bed

After reaching the uterine cavity the fertilised ovum passes by some process, the nature of which we still imperfectly understand, into the subepithelial tissue. By some it is supposed to burrow through the smooth surface of the endometrium (Peters, Graf v. Spee, Leopold, etc.); by others it is believed to settle in a small depression on the mucosa surface (Bryce and Teacher), or in a crypt between two folds, such as Hubrecht has described in the case of the hedgehog.

To reach the subepithelial tissue it is clear it must destroy the superficial epithelium. The degree of this destruction is probably small. Whether it is due to a phagocytic or to a corroding and dissolving action we are not certain, though, in view of the markedly softening influence which the chorionic elements exert on the maternal tissues, *e.g.* pregnant tube, it is not unlikely that the superficial destruction is accomplished by the latter process. This is especially probable from the fact that recent research would seem to have demonstrated the absence of a phagocytic activity in the cells of the human fœtal ectoderm.

After reaching the uterine stroma it forms for itself a nest consisting of a hollowed-out region of the mucosa, where it is in intimate relation to the maternal blood, from which it abstracts its nourishment. In this place we are especially concerned with the mode in which the cavity in the mucosa is formed and the manner in which the maternal vessels open up to provide the growing ovum with its food. It seems to me that the investigations which I have recorded in the preceding pages provide us with a clue to the explanation of many of the changes present. In many instances in their results the alterations produced in the maternal mucosa by the engrafted ovum coincide accurately with those which we have noted in the abnormal regions of chorionic

activity. In the normal site many of these results are still imperfectly understood, and it seems not unlikely that in their production influences similar to those noted above have been in operation.

For a study of the early changes which the maternal tissues exhibit in response to the presence of the ovum we are provided with several young specimens—those of Peters, Teacher and Bryce, Leopold, Jung, etc. Before giving an account of an early ovum which I have recently had the opportunity of studying, I shall review in brief some of the data supplied by the above ova which are more especially relevant to this work.

Summary of Data Supplied by the Peters, Teacher-Bryce, Jung, and Leopold Ova

Peters' Ovum (1899)

In this we have, thanks to the scientific precision of the descriptions and the excellent accompanying plates, an opportunity of studying the maternal changes, which, I believe, represent the earliest phase of the process described hitherto.

The ovum lies embedded in the mucosa immediately under the surface epithelium, several of the cells of which have disappeared. At its outermost pole it is separated from the uterine cavity only by a cap of blood clot.

The Ovum.—This is a lenticular mass. It measures 2·4 × 1·8 mm. in its external diameters. The longest diameter is parallel to the surface of the mucosa. The surface of the blastocyst is formed of ordinary trophoblastic cells (Langhans') several layers deep. At some regions, especially towards the basal aspect, the cellular layer is thicker than at others. The trophoblast is not solid, but is broken up by a large number of spaces, some of which appear empty, whilst others are occupied by maternal blood. Those lacunæ permeate the trophoblast in a very intricate manner. Some of the cells are vacuolated. The surface of the trophoblast, and, for the most part, the walls of the lacunar spaces, are lined with a plasmodial nucleated material. This corresponds to the syncytium. By Peters this is supposed to be due to a fusion of the Langhans' cells, partly under the influence of the blood-pressure, and partly by the action of the blood plasma. He thinks, also, that degenerated red corpuscles may enter into its formation. In most places the syncytial layer is poorly developed, and certainly is not so evident as is described in later periods of pregnancy. In many places

it is vacuolated. The spaces thus produced may be occupied with maternal blood. The embryo is situated at the basal aspect of the blastocyst cavity.

The Maternal Tissues.—The surrounding maternal tissues are markedly œdematous, and are infiltrated with red blood corpuscles. The œdematous condition Peters attributes partly to the intense vascular congestion and partly to an accumulation of the assimilation products which pass between mother and child. In places it has led to a wide separation of the stroma cells, and they are then seen to be united with one another by long, filamentous, protoplasmic processes. Many of the stroma elements, especially in the proximity of the ovum, are enlarged to form decidual cells. This change has occurred only to a comparatively small extent. It is much less evident than in the Teacher-Bryce ovum and in later periods of pregnancy. Throughout the maternal tissues the œdematous spaces separating the decidual cells are occupied with red blood cells. *The irregular nature of the fluid and blood escape into the tissues is one of the most remarkable features of the Peters ovum.* It is most marked round the ovum, but it is *evident even at a distance from the fœtal structures.* These changes have led to an increase in the thickness of the mucosa in the proximity of the ovum.

The vascular changes are for us especially important. In the area of the mucosa just beyond the site of the ovum there is evident a large number of small vessels. Arteries with their ordinary supporting coats are seen pursuing their way towards the epithelial surface, often in a cork-screw-like fashion, in the partition between the gland spaces, which are dilated in the deeper part to form a spongiosa. *In the immediate proximity of the ovum the outer supporting cells of the vessels become detached,* and they are often seen to be lined by a single layer of endothelial cells. That this condition has affected the arteries is proved by the fact that in this region there is no evidence of the comparatively thick walls which we associate with them. In some places at a greater distance from the ovum we can see the process of detachment in action—at one part of its course the same artery may exhibit the ordinary concentric arrangement of the supporting cells, and at other regions on either side of this we see it denuded of these outer cells and represented only by an endothelial layer.

The most remarkable change in the vessels is the increase in their diameters. *In the proximity of the ovum this has occurred in places to an enormous degree.* On the serotinal aspect of the ovum there is a large blood tract which, on its lower aspect and laterally, has deeply

invaded the surrounding tissues. *It is lined, for the most part, by a layer of flattened cells.* These are absent in some parts. Through its wall it is often possible to recognise the blood cells streaming into the surrounding tissues. From this large blood lacuna there is a row of smaller blood spaces extending round the base of the ovum in a curvilinear manner, like the meridians of a globe. Here and there they open into the lacunar spaces on the chorionic surface.

In the proximity of the ovum the blood spaces have, as the result of their expansion, come right up against the chorionic surface, and are separated from this only by an endothelial layer. In many places this is lost, and the vascular contents thus bathe the chorionic surface directly. In this region there is evidence of rupture of the endothelial layer, with a liberation of the blood into the embryonic lacunæ. Peters thinks that this is due to the intravascular pressure, predisposed to by a thinning out of the vessel wall, and a degenerative softening change in the endothelial remnants. *Extending across the spaces intervening between the expanding vessels and the chorionic surface there has been in many places an escape of the fluid and corpuscular elements of the blood.*

There are, in respect of the above vascular changes (those in italics), striking resemblances between the changes present here and those which we have detected in the pregnant tube and in the chorion-epitheliomatous uterus. The similarity between the response of the maternal tissues in these differing conditions is still further emphasised by the discovery in Peters' specimen of another vascular change, which we have already recognised in the above abnormal sites of the fœtal elements. This is found in the shape of a *formation of new capillary vessels* round the periphery of the ovum. According to Peters, in the mucosa round the trophoblast the new vessels have apparently been formed chiefly by a projection of buds from the original vessel walls. These become canalised and occupied with blood. These newly built capillaries, at first quite narrow, widen and come into contact with the trophoblastic buds as they grow into the spaces of the œdematous stroma. Peters states that this new vessel formation can have only one object, namely, that of carrying blood to the peripheral layers of the trophoblast.

The Teacher-Bryce Ovum (1908) (Fig. 59)

The Ovum.—In its external diameters this measures 1·95 × ·95 × 1·10 mm. It lies in a cavity of the mucosa, just under the surface

epithelium. This has been detached. At its outer pole there is a small dimple, probably corresponding to the site of entrance. There is no fibrin cap such as is present in Peters' ovum. The blastocyst wall is composed of a uniform layer of trophoblastic cells, and, external to this, by a large and irregular mesh-work formed by plasmodial strands. This, in places at its outer part, lies up against the walls of the gestation cavity. The meshes are formed by spaces of varying size in the plasmodium. The larger spaces are towards its outer aspect. Some are apparently empty, whilst others are occupied by maternal blood. According to Bryce and Teacher these spaces are, to begin with, probably formed by the accumulation of digestive juices which escape and allow of the entrance of the maternal blood. It will be noted that the syncytial development is, in this specimen, much more evident than in Peters' case. The embryonic rudiment is considerably distorted, and occupies a central space formed by a shrinkage in the mesoblast.

The Maternal Tissues.—The ovum lies in a cavity formed in the superficial part of the mucosa, which is thickened, and projects somewhat into the uterine cavity as a "decidual lobule." The walls of the implantation cavity are, for the most part, smooth all round. There is, in this respect, a marked difference between the present specimen and that of Peters, where the confines of the chamber are irregular in nature, and in many places straggle into the adjoining tissues. There is a well-marked decidual formation round the ovum cavity. This has resulted in the production of large, densely packed cells, somewhat similar to those found in the decidual membrane of a later date. The surface of the decidual tissue immediately opposed to the implantation cavity is markedly necrosed. It is represented by a "hyaline, darkly-staining, and nearly nuclear-free zone." This appearance, as we have seen, is absent in Peters' specimen. The blood-vessels of the decidua are greatly dilated, and in many places, especially under the blastocyst, there has occurred extensive hæmorrhages. In one part of the sections the necrotic zone of the decidua is broken up by a hæmorrhage. On the basal aspect of the decidua the dilated vessels have formed the "blood cushion" similar to that seen in the case of Peters' specimen, and also in an early ovum described by Graf v. Spee. Whilst there is marked hæmorrhage throughout the adjacent maternal tissues, it is not present to nearly the same degree as is exhibited by Peters' ovum. There is not the same widespread infiltration of the immediately adjacent tissues with fluid and blood, and the blood-

vessels, though expanded, are in the immediate vicinity of the gestation cavity often seen to possess well-defined walls.

The decidual reaction in this specimen would seem, from the plates, to be more marked than in that of Peters. In the latter it is present to a degree less evident than in any other specimen described, whilst in the former it is seen in a manner closely suggesting the structure of the ordinary decidual membrane of a later date. If Peters' specimen be normal it is clear that, from this point of view, the Teacher-Bryce specimen would correspond to a later phase of the maternal reaction.

The Embryo.—In the Bryce-Teacher ovum the embryo is considerably distorted and somewhat broken up. In spite of this a careful examination of the component parts has enabled the two observers to recognise in it the earliest phase of the human embryo ever described.

Jung's Ovum (1908)

The measurements of the blastocyst are $2{\cdot}5 \times 2{\cdot}2 \times 1$ mm. In many respects this specimen corresponds to the ovum of Peters. There is, however, a better development of the villi, and Teacher and Bryce, in their calculation of the ages of the different early ova, have placed this at $14\frac{1}{2}$-$15\frac{1}{2}$ days.

In the marginal zone of the decidua there is a fibrinous or hyaline degeneration of the tissues similar to that in the necrotic zone of the Teacher-Bryce specimen. The cells are seen in all stages of the degenerative process. This zone is richly infiltrated with blood corpuscles, red and white. In the tissues surrounding this region the vessels are distended, and there are many capillary vessels present. The decidual cells are spread apart by œdema, and they are seen to be united with their neighbours by long protoplasmic strands. In this way a reticular structure, similar to that present in Peters' ovum, is produced. In the meshes red and white corpuscles are found. Jung challenges Peters' description of the formation of new capillaries. He states that his specimen exhibits appearances similar to those described by Peters, but that what look like newly formed capillaries are really intercellular spaces containing red blood cells, or they are larger vessels whose walls have been compressed till the opposite walls have been brought into apposition. In the *Umlagerungszone* there is a well-marked formation of decidual cells. External to the necrotic zone numerous mitotic figures are present.

Leopold's Ovum (1906)

This corresponds closely to Peters' specimen in the mode of attachment of the ovum to the uterine mucosa. Here there is again a well-marked vascular distension and hæmorrhagic and fluid infiltration of the tissues in the *Umlagerungszone.* The surface of the blastocyst is markedly torn up, and there is no embryonic rudiment visible.

DESCRIPTION OF AN EARLY HUMAN OVUM

This specimen was discovered accidentally in a portion of decidua sent to the Royal College of Physicians Laboratory for examination on the 1st April 1910. The early ovum was detected in one of the sections, and, through the kindness of Dr. James Ritchie, it was handed over to me for further examination. A number of the sections containing the ovum were unfortunately lost, but, as I shall subsequently point out, it would seem more than likely that in the part rescued we have the greater part of the ovum, and that we are in a position to estimate its maximum diameters. As soon as the value of the specimen was recognised the portion of the paraffin block containing it was cut into an uninterrupted series of sections. By this means I have been able to obtain forty-two sections containing the ovum. These were stained for the most part with hæmatoxylin and eosin. The preservation, considering the manner in which it was obtained, is fairly good.

History.—The specimen was obtained from a patient aged 21. The last menstruation commenced on the 22nd February. The period due on the 21st March was missed. On the 31st March she complained of a slight bleeding discharge, and on the morning of the 1st April passed the decidual fragments, in which the ovum was discovered. Previous menstruation somewhat irregular. No definite history as regards coitus obtainable.

General Description of Specimen

This consists of three pieces of thickened mucosa and some blood-clot. Two of the fragments are extremely irregular in shape, and in the course of the sections are seen to be somewhat broken up into different pieces. The portion of the mucous membrane containing the

imbedded ovum, on the other hand, is more regular in shape. It is an elongated oval in contour, rounded off at one end (Plate XIV.), whilst at the other it tapers off into a fine strand of the mucosa. As the sections are followed the oval becomes increasingly smaller until it ultimately disappears. After a few sections are passed, also, the tail-like process becomes lost. From this description it is, I think, clear that we are dealing with the elevated lobule of decidual tissue which corresponds to the similar structure present in all the other early ova (Teacher-Bryce, Peters, Leopold, etc.). In cutting the block the first sections correspond to the base of the lobule and have shaved the surrounding mucous surface (corresponding to the tail). The succeeding sections cut the lobule across at more and more superficial levels until it is ultimately lost altogether.

The Decidua.—In the outlying portions of mucosa there is an almost complete absence of a decidual change. In places, especially towards the more superficial parts, the stroma cells are enlarged. For the most part, however, they have retained their normal size. Throughout the entire extent of the mucosa there is a well-marked œdematous exudate, and in many places a hæmorrhagic infiltration of the tissues. There is also an evident escape of leucocytes. The epithelium of the glands and surface has in most places been shed.

In the decidual lobule in which the ovum is placed the same general features are present. Here there is a shedding of the superficial epithelium and of that lining many of the glands. The gland spaces are in places markedly expanded. In the lobule the implantation chamber containing the ovum is placed. It is shut in by a thin shell of the mucous membrane, and is placed more toward the pole of the cut lobule which corresponds to the rounded free end at the base. The characters and size of the chamber and the ovum and some remarkable appearances which are divulged in the course of the serial sections will be discussed in the next paragraph.

I propose to describe the details in the following order:—

1. The implantation chamber and the ovum.

2. The mode of imbedding of the ovum as revealed by a study of the serial sections.

3. Changes in the surrounding tissues—The decidual reaction—Cause of the blood escape from the vessels.

4. The age of the ovum.

The Implantation Chamber and the Ovum

As in other early ova, the *implantation chamber* is drawn out parallel to the surface of the mucosa. Its measurements, so far as the specimen permits of their being taken, are :—

Maximum length	1·5 mm.
Maximum breadth	·97 mm.

In shape it is almost a perfect oval. Its size is much greater than that of the contained ovum. In a section cut across the decidual lobule towards its broader and longer aspect, *i.e.* the base, the ovum is seen lying in the cavity for the most part unattached (Plate XIV.). It is surrounded on all sides by fresh blood, which occupies the remainder of the cavity.

The *ovum* consists of a somewhat irregularly shaped blastocyst. The surface is thrown into a number of depressions and elevations, the latter corresponding to rudimentary villi. At some places the villi are better developed than at others.

At the region of the base of the lobule the measurements are—

Length of blastocyst	1·125 mm.
Breadth „ „ (at widest) . .	·67 mm.
Breadth „ „ (at narrowest) . .	·075 mm.

As already mentioned, a part of the ovum is wanting, and it is therefore impossible to give the other dimension. As the sections which were rescued are traced in series, it is found that the breadth of the blastocyst gradually increases to a maximum (·7 mm.) and then gradually diminishes. This indicates that we have in the sections the greatest diameter in one direction. The length of the blastocyst in the section corresponding to this maximum breadth is appreciably smaller than that given above (1·125 mm.). This would seem to indicate that the ovum has been cut across slightly diagonally. These considerations, in any case, demonstrate, with a distinct measure of certainty, that in this specimen we are dealing with a very early ovum. The approximate age I shall refer to later.

The surface of the blastocyst, except at one part which will be referred to subsequently, possesses the usual epithelial covering. With hæmatoxylin and eosin stains no distinct differentiation into layers is detected. With special stains, however, the epithelium is seen to consist of the usual Langhans' layer, which rests on the tissue of

the mesenchyme—the cytoblast (van Beneden) or cytotrophoblast (Hubrecht, Teacher and Bryce). External to this layer there is the syncytium, plasmodiblast (van Beneden), plasmodium, or plasmoditrophoblast (Hubrecht, Teacher and Bryce).

The *cytotrophoblast* is one, two, or more cells deep. In places solid masses of cells project from the surface of the blastocyst somewhat similar to the appearance present round the circumference of the Peters and the Jung ova. In my ovum this condition is present to a much less degree than in either of these specimens (Plates XIV. and XV.). In some few places one can recognise the existence of distinct cell boundaries; these are especially evident in the projecting masses. In most places, however, there is a complete absence of the cellular distinctions, and the immediate boundary of the blastocyst seems to be composed of a nucleated plasmodium. When stained with eosin and methylene blue the cell substance is of a purple colour. The nuclei are large, and in places exhibit a distinct reticular structure.

The *plasmoditrophoblast* consists of strands or masses of multinucleated protoplasm. These form sheets of varying thickness placed on the surface of the cellular layer, or they take the form of solid columns or buds which are circular or oval on section, and which jut into the implantation chamber. Unlike the cytotrophoblast, this layer is characterised by an extreme irregularity of disposition. Whilst in some places it is heaped on the surface of the blastocyst, in other places the cellular layer is left devoid of a syncytial covering (Plate XIV.). With the eosin methylene blue stain the plasmodium is deep red.

In places a sponge-like arrangement can be detected in the protoplasm. In some regions there is a vacuolation, and in the spaces thus formed red blood corpuscles may be present. In no place is there any evidence of the complicated reticular disposition of the plasmodium which Teacher and Bryce noted in their specimen. The nuclei are, on the whole, smaller than those in the subjacent layer, and they for the most part absorb the stain uniformly throughout their substance. In some few places isolated syncytial buds are seen lying up against the necrotic zone of the decidua; in other regions the fœtal cells lie free in bays excavated in this zone (Plate XV.).

Scattered about the implantation cavity islands of chorionic cells are seen, apparently detached from the blastocyst. If these are traced in series, however, they are seen to amalgamate with the solid masses of cells which project from the fœtal surface. In some places, especially towards the wall of the implantation cavity, large mononucleated cells

are present, similar to those described by Hubrecht, Teacher and Bryce, Peters, Graf v. Spee, and others. These are probably fœtal in origin.

As in all early ova, with the exception of that described by Teacher and Bryce, the surface of the blastocyst is thrown into a considerable number of elevations and depressions. The elevations consist for the most part of simple, unbranched stalks of mesenchyme covered by an epithelial layer. In some few places lateral off-shoots from the main stalk may be present. One or two of the larger projections are continued outwards as masses of cells devoid of a mesodermic core. These two latter appearances are much less evident in my specimen than in those of Peters and Jung (Plates XIV., XV.).

An appearance of interest is seen all round the circumference of the blastocyst surface. This is illustrated in Plates XIV. and XV., where adjacent villous projections, instead of arising separately, are seen to be fused together by solid masses of the chorionic cells of varying thickness. In the main the intervening cell columns are quite narrow; in some places they consist in section of mere streaks of tissue. These appearances, which at first might suggest that there has been a secondary projection of the ectodermic cells into the mesodermic core of the early villus or of the blastocyst cavity, are probably due to the fact that the mesodermic growth has occurred in these places into originally solid masses of the epithelium, which are now represented by the cellular covering and the intervening cell columns. On the other hand, it is possible that these latter correspond to a fusion of the epithelial surfaces of two rudimentary villi which lie apposed to one another.

Contents of the Blastocyst

The cavity of the blastocyst is occupied by a mass of branching mesenchyme cells. The adjacent cells are united by slender protoplasmic strands, which often attain a considerable length. The spaces of the network thus formed are occupied by a finely granular material, suggesting a coagulum. With the exception of several small clear spaces towards the centre of the blastocyst in some of the sections, which have been produced by a shrinkage, the mesenchyme fills the entire cavity of the blastocyst (Plates XIV., XV.). There is no trace of a cleavage into two layers, and it clearly corresponds to an earlier stage than that present in the Peters, Jung, and other early ova, where the mesenchyme is distributed on the surface of the blastocyst cavity as a narrow, dense layer. In this respect my specimen coincides with the conditions present in the Teacher-Bryce ovum.

As already stated, the mesenchyme has become projected outwards all round the surface of the blastocyst as rudimentary villi.

There is no trace of embryonic rudiment in any part of the blastocyst, either in the cavity or in relation to the wall. The fact that the Teacher-Bryce specimen, which is the earliest stage of the human blastocyst ever discovered, possesses distinct evidence of the developing embryo in the form of two epithelial vesicles — amnio-embryonic and entodermic—would seem to indicate that the condition in my specimen is abnormal. It is now well recognised that a blastocyst may occasionally develop without an embryo; a considerable number of cases have been described at a later stage than this specimen (*e.g.* that of Leopold, 1906).

Mode of Imbedding of the Ovum

In Plate XIV. it is seen that the blastocyst is nearer the wall of the implantation chamber on the aspect which corresponds to the "free" surface of the decidual lobule than at the opposite pole. This relation it holds throughout the sections. As the sections are followed in series, it is found that this portion of the ovum becomes attached to, and then projects progressively more and more into, the decidua, until it ultimately comes to project on the free surface of the mucosa. On either side the walls of the chamber, which are here in contact with the ovum, become more and more thinned out over the rounded aspect of the blastocyst until they ultimately disappear. Here the blastocyst, denuded of its epithelial surface, is in direct relation to the uterine cavity (Plates XV.-XVIII.). As the sections are pursued, the part of the implantation chamber which accommodates the exposed pole of the blastocyst becomes more and more cut off from the larger part of the cavity by an inward projection of two lateral portions of the degenerating marginal lamina of the decidua. These are seen in Plate XVI. as two beaks, which project towards one another, and between which there is the narrow strait separating the outer and smaller part of the chamber from the inner and larger. The blastocyst becomes gradually more and more constricted at the region corresponding to this position. In some places it is divided into two portions by a narrow neck. Further on this disappears, and the blastocyst then seems to be completely detached into two separate parts, which become smaller and more and more widely separated as the sections are traced (Plates XVI.-XVIII.). Eventually the decidual beaks fuse to form a partition of darkly staining degenerating tissue,

which completely separates the two parts of the implantation chamber. This partition becomes broader and broader as the sections are traced in series. At the same time the two parts of the chamber, with the contained pieces of the blastocyst, shrink until they ultimately disappear, the inner before the outer (Plates XVII., XVIII.). The terminal sections containing the ovum reveal the remarkable appearance seen in Plate XVIII. Here the exposed portion of the blastocyst is very small, and is completely separated from the main mass of the decidua, which has now shrunk to meagre dimensions. This region of the blastocyst is devoid of an epithelial covering, the darkly staining covering on its upper aspect in the figure corresponding to the attenuated portion of the necrotic lamina of the decidua.

The remarkable condition just described, which, so far as I know, has never been noted before in an early ovum, is clearly amenable to one interpretation only. The outer pole of the blastocyst is projecting on to the surface through a small aperture in the wall of the implantation cavity. This explains the gradual approximation of the sides of the decidua as the sections are followed. The apparent separation of the chamber and blastocyst into two portions is dependent on the fact that the outer part of the ovum is bent at an angle to, and is folded over, the main portion. This condition is already visible, even when the sections reveal the ovum entirely in the implantation cavity (Plate XIV.), and, in view of the facts subsequently described, it is now easily understood. In view of this interpretation of the appearances, also, it is clear that in Plate XV. the aperture in the decidua is cut in the long axis, whereas in Plates XVI., XVII., XVIII. the section is transverse or obliquely transverse. The apparent increase in thickness of the darkly staining partition intervening between the two parts of the implantation cavity (Plate XVII.) is due to the fact that the wall of the opening is cut across obliquely in the sections.

Whilst the appearances described above lend themselves to a comparatively easy anatomical explanation, greater difficulty is encountered in an attempt to extract the ultimate meaning of this remarkable situation of the blastocyst. This would seem to fall under one or other of two explanations: (1) that the roof of the implantation chamber has given way, either as the result of an erosion by the chorionic epithelium, or from some other cause, allowing an extrusion of this pole of the ovum, or (2) that the structural arrangements exhibit the steps in the process by which the ovum, after destroying the surface epithelium, works its way into its bed in the subjacent tissues.

Whilst the initial stages of the imbedding process in the human ovum are still undiscovered, it is impossible to state with certainty at what point of development the epithelial destruction, which precedes the formation of the nest in the mucosa, occurs. Comparative embryology would indicate that in animals this may take place whilst the ovum is still a minute structure. In the guinea-pig, for example, the entrance occurs whilst the ovum is in the early blastocyst stage (Graf v. Spee). It seems probable that in the human a somewhat similar condition holds. At any rate, data derived from the earliest detected phases of the process indicate that the amount of epithelial destruction necessary before the ovum can reach the subepithelial tissue is very small (*e.g.* Peters').

In the Teacher-Bryce ovum the wall of the decidua is complete all round the implantation chamber. The portal of entrance would seem to correspond to a minute orifice in the region of a minute dimple on the surface of the mucosa, ·1 mm. in diameter; it is sealed by thrombus-like material. On either side of this there is a distinct layer of decidua in the roof of the ovum cavity. In the ova of Peters and Jung the point of entrance corresponds to an aperture closed in by a cap of fibrin and blood-clot. It is relatively wider than that present in the Teacher-Bryce specimen, and these authors have inferred that the extent of the gap warrants the conclusion that it "is not the portal of entrance properly so called—it is much too large—but is a secondary formation, being produced by the subsequent destructive activity of the trophoblast threatening to destroy the roof of the implantation chamber." In my specimen there is no trace of any fibrin or blood cap, but the relatively large aperture is effectually plugged by the outer pole of the ovum. I have referred to the fact that the edges of the opening fit so closely round the blastocyst that there is no space left between them.

I would submit the following considerations in support of the view that the situation occupied by the outer pole of the blastocyst is to be explained, not by supposing that the wall of the implantation chamber has been secondarily destroyed in this region, but rather that the aperture is present because of a failure of the lips of the decidua to grow across behind the engrafted ovum, such as must occur normally, to close in the aperture of entrance. It will be noted that the exposed surface of the blastocyst is smooth. It is devoid of the villous projections which characterise the wall of the ovum where it is situated within the blood lake. Although the epithelium in the outer part is detached, it is easy to follow round the smooth surface of the blastocyst, indicated by a definite line corresponding to the surface of the exposed mesenchyme.

The absence of the villi would identify this part of the blastocyst with the avillous state of the early ovum, and it would suggest strongly that this portion of the blastocyst had been lying in its present site a considerable time before the innermost portion had assumed its comparatively well developed state. It is difficult to imagine how the outer pole could have failed to develop villi if the position which it occupies had been dependent on a gradual expansion of the blastocyst, with a destruction of the superjacent tissue, or on a gradual extrusion of the blastocyst from the implantation chamber, say due to the pressure of the blood in the cavity. On the other hand, if this position correspond to that primarily occupied by the early blastocyst, it is easy to understand why the expanding wall should have retained its smooth contour in this region; the absence of the necessary blood supply would prevent any development. That this is the true explanation is seen in the fact that the epithelium and mesenchyme are seen to sprout in the form of villi immediately within the blood space.

I shall subsequently point out that the maternal tissues in this specimen reveal little evidence of a decidual change. It would seem certain that, under normal circumstances, the opening made by the ovum in the mucosa is quickly closed up by a swelling and approximation of the lips due to the cellular proliferation and enlargement associated with the decidual change in the stroma cells. In view of this, we can understand that where there is a ready response on the part of the maternal tissues to the influence of the ovum the gap will be more speedily obliterated (Teacher-Bryce ovum) than where, for any reason, the decidual reaction is tardy (Peters ovum). The fact that, although the Peters specimen and that here described clearly correspond to older stages of the blastocystic development than that of Teacher and Bryce, the decidual transformation is much less evident in the former would suggest that there must exist in the stroma elements of different individuals, and perhaps of the same individual at different times, varying degrees of susceptibility to this decidual change. I would suggest that in these considerations resides an explanation of the differences detected in the different early ova. Even if this be so, however, it cannot be denied (and this I shall discuss more fully on a subsequent page) that the decidual alteration in the cells is instrumental in preventing the destruction of the maternal tissues, and that, where this change is poorly marked, as in the Peters ovum, it is conceivable that an erosion of the roof of the implantation cavity by the fœtal cells might result in an increase in the gap, such as Teacher and Bryce suggest.

I believe, however, that once the decidual change becomes clearly established, as in the Teacher-Bryce ovum, the roof will not only withstand the destructive action of the chorionic cells, but it will become progressively thicker.

We may here pause to consider a suggestive analogy with the conditions exhibited by this ovum presented by the manner in which a villus in the pregnant tube, after passing through the wall of a maternal vessel, continues to develop within the lumen. When the tip of a villus reaches a vessel (or even whilst it is still at some distance, as I have shown in Chapter III.) the wall gives way. When this occurs the rich blood supply provided may lead to a luxuriant growth of the villus within the vessel lumen, along which it may spread for a comparatively great distance (Fig. 35). It would seem not unlikely that a somewhat similar process may take place in the imbedding of the ovum. As I shall subsequently point out, it is probable that, by the time the removal of the epithelial cells necessary for the imbedding process has occurred, the changes in the subjacent maternal tissue have resulted in a flushing of the part with the nourishing blood fluid. Into this region, as in the case of the vein with the villus, the early blastocyst will quickly grow. It will expand in all directions in the subepithelial tissue till it attains the size represented in the earliest known ova. Meanwhile the approximation and fusion of the lips of the small opening behind the ovum will lock the door by which it had entered. The mode of formation of the implantation chamber I shall refer to later.

This interpretation of the process is confirmed by the conditions present in my early ovum. These suggest that the blastocyst has reached its bed in the subepithelial tissue entirely by a *growth* inwards. The deficient decidual change has resulted in a very imperfect approximation of the lips of the opening behind the ovum, with the results which have been described.

This description of the process is very similar to that advanced by Peters. It possesses the advantage of explaining how the ovum may readily reach the stroma even if it land on a level part of the mucosa. It must, I think, be admitted that the data derived from other early human ova would seem to preclude the possibility of explaining the position of the blastocyst as being dependent on a landing in a furrow, the edges of which have closed behind, as in the hedgehog. There is equally little evidence in favour of the view that a development in a depression of the mucosa is necessary. The difficulty clearly in

explaining the site of the implantation cavity is that, unless a depression be postulated, a wholesale *displacement* of the early ovum through the surface region of the mucosa would seem to be necessary. In view of the considerations advanced above, however, this difficulty is overcome by realising that a growth of the surface of the blastocyst in the direction of the blood may occur. The swelling of the mucosa superficial to the ovum will lead to an expansion of the cavity in an outward direction. This accounts for the space present between the blastocyst and the roof of the implantation chamber in the early ova. It will thus tend to lift the roof of the chamber away from the ovum, and enable the gap to become sealed after the early blastocyst has been surrounded on all sides by the blood lake.

Briefly I would summarise as follows the conclusions which a study of my early ovum, taken in conjunction with the other specimens, would seem to warrant in regard to the manner in which the ovum reaches its bed in the subepithelial tissue of the mucosa. At the spot selected for the imbedding, the fœtal cells destroy several of the epithelial cells of the mucosa, which may be at the region perfectly smooth on the surface. The removal of the cells is probably dependent on a splitting up and solution of their substance, which the fœtal cells are able to effect by virtue of a liberated extracellular material. It is likely that the epithelial removal is greater than the size of the entering ovum. It would seem likely that at the same time, or even before the epithelial shedding has occurred, this fœtal material diffusing into the maternal tissues leads to a spreading part of the superficial regions of the stroma by lymph and perhaps by blood cells. This preparation of the mucosa for the reception of the ovum, even before it has reached the stroma, to which I shall refer in greater detail on a later page, would correspond to the changes exhibited by the tissues of the pregnant tube, etc., in advance of the chorionic cells and clearly due to the diffusion of some substance into the tissues. They would, in addition, correspond to the well-recognised fact that in many of the lower animals a similar flushing of the mucosa with fluid and blood is often noted clearly before any attachment of the fœtal cells has taken place. After the epithelial shedding has occurred the blastocyst grows into the subepithelial tissues, *i.e.* in the direction of the blood. There it continues to enlarge in all its diameters in the ever-increasing blood cavity. The walls of this draw away on every side, and the decidual increase in the roof of the cavity soon leads to an obliteration of the portal of entrance. In my specimen the stages of this process are

exhibited. In view of these considerations it is suggestive to find that in Leopold's earliest ovum (1906) there is a mass of fœtal tissue surrounded by blood and imbedded in the decidual tissue which corresponds to the point of entrance of the ovum. It is completely separated from the main blood cavity, and in some of the sections it looks like a diminutive implantation chamber. Just under it the surface of the blastocyst is adherent to the wall of the ovum cavity by means of a stalk of trophoblast, and the appearances suggest that the conditions present may be due to a shutting-off of the superficial part of the implantation chamber with a portion of the ovum by apposition of the lips of the gap, somewhat similar to what seemed to be happening in my specimen.

Changes in Maternal Tissues—Decidual and other Alterations in Stroma Cells — Cause of Blood Escape from the Vessels

The Marginal Zone.—The mucosa bordering on the implantation chamber exhibits a marked degenerative change. This marginal necrotic zone extends completely round the implantation cavity; it is well shown in Plate XIV. On the aspect facing the blood space the degenerative change has progressed to the degree of almost completely obliterating the cell features. Here there is little visible but a darkly staining tissue, with a disappearance of the cell boundaries and the nuclei. In some places, imbedded in this, large deeply staining cells are visible with nuclei, which may be well preserved, but which, in the large number of cases, exhibit different grades of the disintegrative process. The necrotic tissue forms a homogeneous mass, or it is beset with clear spaces to form a sort of reticulum, in which red blood cells and leucocytes are plentifully scattered. Further out the necrotic changes become less and less evident, until they disappear altogether. As before, there is the same infiltration with blood corpuscles. In this region the steps in the degenerative change in the cells is clearly traceable. The stroma cells are found to become markedly swollen. This increase involves the cell body more than the nucleus. At the same time the cytoplasm stains deeply with eosin and exhibits a granular appearance, or, in some cases, a curious character somewhat resembling that presented by opaque glass. These changes, which clearly correspond to the penultimate stage of the necrotic process, are thrown into relief by contrast with neighbouring stroma cells, which, though markedly swollen, do not present the same staining characters.

In many places the inner edge of the necrotic zone is ragged, and it presents appearances which suggest that it is becoming broken off in fragments into the ovum cavity. At the pole of the chamber, which has been cut across tangentially, the interesting appearance represented in Plate XVII. is noted. Strands of tissue staining deeply with eosin are seen to be stretching into the blood space, sometimes in a radial manner; they are often seen to extend as far as the surface of the blastocyst, which in this region is reduced to meagre dimensions. This tissue is attached at its outer aspect to the necrotic zone of the decidua, with which it corresponds in every respect. Sometimes in the substance of the strands one can detect nuclei in various stages of disintegration. This appearance suggests that the ragged edge of the marginal lamella of the mucosa may be due to a detachment of strands of this nature. The significance of this—whether it is artificial or not—it is impossible to tell with certainty. In many places the necrotic tissue exhibits the formation of clear spaces or vacuoles in its substance.

In some few places fœtal cells may be found close to the necrotic tissue. In Plate XV. is seen a mass of syncytial tissue projecting into a bay excavated in the wall of the implantation cavity.

Decidual Changes in Stroma Cells

In the "decidual lobule" many of the stroma cells are swollen. The increase in size involves chiefly the cell body, which, as in the cells to which I have referred in connection with the necrotic zone, often exhibit an appearance similar to ground glass. Some of the cells attain a size which identifies them with the ordinary decidual cell of a later date of pregnancy. These decidual cells are found of this size only in the proximity of the ovum chamber. Even in this site the change has involved to this extent only stroma cells scattered here and there. They are never found packed together in masses as at a later date, or even as is represented in Peters' early ovum. There is no change in my specimen, in addition, which corresponds to the decidual tissue present in the Teacher-Bryce ovum. Between the markedly enlarged cells the stroma elements show all stages of the change; for the most part, however, the increase in the cell body is in the initial stages. Beyond the stroma which encircles the implantation chamber the enlargement of the cells is still found for some distance, gradually fading away as the region of the ovum is left. In all these regions the stroma cells are spread apart by an œdematous exudate. The enlarged and the unchanged cells are united by protoplasmic filaments and in

the spaces between them large numbers of red and white blood corpuscles are present. The blood is streaming into the tissues through the vessel walls (Plate XIV. and Fig. 60). These changes I shall refer to in greater detail later on.

In *the outlying parts of decidua* the stroma elements are for the most part normal in size. Here and there, towards the surface of the mucosa, they are enlarged, but they never exhibit any more than the initial stage of the decidual increase. In many places the enlarged cells are spindle shaped. In many regions there is an œdematous and hæmorrhagic infiltration of the tissues, with a spreading apart of the stroma cells. These changes are most marked in the surface layers of the mucosa.

In the decidual lobule, as in the outlying decidua, the *epithelium* is removed from the surface, probably by a process of maceration. In most of the glands the same has occurred. In some places the detached cells are lying in the gland lumina.

Changes in the Stroma Cells and the Vessels, and the Cause of the Fluid and Blood Escape

In view of the investigations recorded in the preceding part of this research the changes in the vessels and the manner in which the blood is escaping are of especial interest and importance.

There is a distension of many of the vessels; this is especially the case in the broad part of the decidual lobule which corresponds to the side of the implantation chamber (Plate XIV. and Fig. 60). Here there is a number of expanded vessels, whose walls are very fine, being formed only by one or two layers of cells. This condition corresponds to the vascular change detected in the Peters ovum.

This thinning of the walls of the distended vessels is due to the fact that there has been a wholesale detachment and displacement of the surrounding stroma elements. These blood spaces thus correspond to the sinuses or distended capillaries which I have described in full in connection with the menstruating mucous membrane (Chapter II.). In structure and in mode of formation they are identical, so far, at any rate, as the grosser structure is concerned. In other respects, also, the resemblance is emphasised. In the first place the opening up of the stroma and vessel wall has, in many places, resulted in the creation of a complete gap between vessel lumen and surrounding tissue (Fig. 60). The ease with which these changes occur in the uterine mucosa is, as I have recorded in a previous section, dependent on the peculiar structural

conformation which it presents. In addition to these changes there is seen to be a wholesale exodus of the red cells through the wall into the surrounding tissue. The corpuscles are streaming out in every direction, both through the incompletely opened-up regions and at those places where there is a complete breach in continuity (Fig. 60).

The blood leakage from the vessels is, as I have stated, found at a distance from the implantation chamber and where there are no fœtal cells. In fact, as I have noted on a preceding page, at no point except at the marginal necrotic area of the wall of the ovum cavity was there any evidence of an incorporation of the fœtal cells with the maternal tissue. Even here it is only rarely encountered. These facts thus force us to the conclusion that the opening up of the maternal vessels during pregnancy, with the consequent hæmorrhagic escape, is due to some influence apart from a direct cellular invasion of the vessel wall with a mechanical escape of the contents.

The resemblance between the conditions encountered in the pregnant tube, etc., and those present here is emphasised in a degree which is most convincing by the discovery that from the vessels opened up in the way I have just described the blood cells are actually seen to be streaming in quantity through the maternal tissue intervening between the vessel lumina and the implantation chamber. I maintain that these appearances prove beyond doubt what my previous researches had led me to affirm, namely, that the orthodox conception of the manner in which the growing embryo is furnished with the mother's blood must be completely modified. It is not due to a destruction of the vessel walls by the invading chorionic cells, neither is it due to a mechanical giving way of the vessel wall where this comes up against the advancing trophoblast (Peters). On the contrary the appearances just described prove that in the process there is in action some change in the vessel wall or tissue leading to a wholesale leakage of the corpuscles, even through a wall which is not yet completely teased out, and *an actual advance of the blood towards the ovum.* In only a few places are the vessels seen to be opening directly into the implantation cavity.

As I have already stated, the mucosa elements in the proximity of the ovum are spread apart by a fluid and blood escape. In the process there has been produced the appearance of the intricate tissue "network," consisting of a large number of what seem to be fine threads united together to form a complex spongework, which I have described in detail in connection with the menstruating mucosa. In Chapter II. I have shown that this structure is to be taken as an index of an active

diffusion into, and imbibition by, the stroma protoplasm of fluid from the vessels. This determines not only the œdematous but also the blood escape. The so-called filaments are in reality films of protoplasm enclosing the fluid. In view of the lengthy discussion which this structure necessitated in the chapter on Menstruation, I would in this place merely state that the structural appearances in the pregnant stroma coincide in every respect with those previously described. There is the same imbibition by the stroma protoplasm, which is beset with a multitude of fluid spaces separated by the fine cytoplasmic films. This change is again especially evident in the perinuclear portions of the cell protoplasm which, in the process, swell to many times their wonted size (Plate XIX.). A disappearance of the partitions leads to an amalgamation of adjacent spaces, and this may continue till large fluid areas are produced. The change is evident right up to the walls of the implantation chamber. The soft, semi-fluid nature of the stroma substance explains at once the ease with which this dragging of fluid from the vessels takes place and the readiness with which it is associated with an escape of the red blood cells (Chapter II.).

In the next chapters I shall discuss in further detail the importance of the investigations recorded in the previous chapters taken in conjunction with these discoveries in regard to the mode of formation of the implantation chamber, the explanation of the formation of the blood sinuses, the function of the decidua, etc.

Age of the Ovum

As the history which is given reveals little of use in regard to coitus we are forced, in our endeavour to place the age of this specimen, to compare its structural features with the other early ova to whieh a fairly definite age can be given. For a scientific discussion of the age of their own and other early ova we are indebted to Teacher and Bryce. I propose to accept the data as stated in their admirable monograph. The ages which they attribute to the following early ova are—

Teacher-Bryce	13 to 14 days.
Peters	$13\frac{1}{2}$ to $14\frac{1}{2}$ days.
Jung	$14\frac{1}{2}$ to $15\frac{1}{2}$ days.

In the specimen which I have described there is no embryonic rudiment, and, from this point of view, we are therefore unable to compare it with those mentioned above.

(1) The blastocyst corresponds to that in Teacher and Bryce's

ovum, and differs from the others in the fact that the *mesenchyme* fills the entire cavity. It shows no sign of cleavage, and it is not disposed, as in the Peters and Jung ova, as a thick layer at the surface.

(2) The *surface of the blastocyst* corresponds to a later phase than the Teacher-Bryce specimen in possessing distinct villous projections, but these are less numerous and, on the whole, smaller than in the two other ova. In addition, the villi are simpler and there is an absence of the cellular masses extending from the blastocyst to the wall of the chamber which are exhibited by the Peters and Jung specimens.

(3) The blastocyst in my specimen is relatively much smaller than the implantation chamber. In this respect it differs from the Peters and Jung ova, where the greater part of the cavity is occupied, and it corresponds to the Teacher-Bryce ovum, where the blastocyst is markedly smaller than the blood space. The conditions found in my ovum might be conceived to be those which would be exhibited by the Teacher-Bryce specimen with a disappearance of the extensive plasmodial development and an increased growth of the surface of the blastocyst. The plasmodial arrangement in their specimen is clearly a temporary structure, and probably disappears after a short time. In addition to this disproportion between the sizes of the ovum and the chamber there is less evidence of a mingling of the fœtal and maternal elements round the margin of the decidua than is found either in the Peters or the Jung ovum.

(4) As I have already noted, the decidual development in my specimen is less evident than in any of the other early ova. Whilst this fact is sufficient to prove that the ovum represents a very early stage, it is of little value in our attempt to allocate to it its exact position in relation to the other young ova, for, as I have suggested, it is not unlikely that the readiness with which the mucosa exhibits the decidual change varies in different cases. This explains an otherwise remarkable finding, namely, that the decidual reaction is less evident in the Peters than in the Teacher-Bryce ovum.

(5) In size my specimen is intermediate between the Teacher-Bryce and the Peters ova. The maximum measurements of the four earliest blastocysts, arranged in their order, are—

Teacher-Bryce . .	·77 × ·63 mm. . .	13 to 14 days.
Young . . .	1·12 × ·67 . .	
Peters . . .	1·6 × ·8 × ·9 mm. . .	13½ to 14½ days.
Jung . . .	2·5 × 2·2 × 1 mm. . .	14½ to 15½ days.

In view of the above considerations I think there can be little doubt

that in the specimen which I have described we possess a link between the stages of development represented, on the one hand, by the Teacher-Bryce ovum, and, on the other, by those of Peters and Jung. If we take the Teacher-Bryce specimen to correspond to the age of 13 to 14 days, which the two authors suggest, the minimum computation for the ovum here described would be about $13\frac{1}{2}$ to $14\frac{1}{2}$ days. If these figures be accepted, and it must be clearly understood that, in the present state of our knowledge of the very earliest phases of growth, they are no more than an approximate calculation, the age of $13\frac{1}{2}$ to $14\frac{1}{2}$ days, provisionally suggested by Teacher and Bryce for the Peters ovum, would require an extension to, say, 14 to 15 days.

CHAPTER VI

EXPLANATION OF UTERINE CHANGES IN PREGNANCY (*continued*)—EXTRACHORIONIC AND INTRACHORIONIC ACTION OF THE FŒTAL CELLS

The Nature of the Chorionic Influence and the Mode of its Spread

The observations recorded in the preceding pages have demonstrated beyond doubt that the degenerative and other changes in the maternal tissues which the fœtal cells induce must be dependent on some substance liberated by them. The fact that the changes are identical in all the conditions studied, and that in the case of chorionepithelioma only the epithelial layers of the chorionic ectoderm are present, proves that this material is derived not from the fœtus or the mesenchyme of the villi, but from their cellular coverings.

What is the exact nature of this substance? The mode of its spread, to which I shall refer immediately, would seem to indicate that it is carried from the fœtal cells in solution, and that it therefore is probably of a chemical nature. Whilst its existence has been definitely recognised by many observers, it is only comparatively recently that the subject has attracted the attention which its importance merits. It has for long been surmised that many of the secrets associated with the toxic complications of pregnancy (hyperemesis, eclampsia, etc.) are bound up with chemical substances produced by the chorionic cells. Whilst in many respects there is a good deal of discrepancy in the results of the different investigators, on one point there is an apparent unanimity, namely, that the placental structures are exceedingly complex in their chemical constitution, and that from them a number of ferments can be obtained *in vitro*. Ascoli, in 1902, described a proteolytic ferment. Bergell and Liepmann, in 1905, demonstrated the existence of ferments acting on carbohydrates (diastase, lactase, and a glycolytic substance) and on proteins. Merletti has also noted a proteolytic material. The presence of a proteolytic ferment was denied by Charrin and Goupil in 1906. Savaré, in 1907, after freeing the placenta from blood, which contains active

ferments, was able to detect both proteolytic and amylolytic ferments, in addition to several others.

While it must be admitted that the subject still awaits further and more convincing elucidation, it is suggestive, especially in view of the investigations I have recorded, to find several of the observers describing the existence of enzymes that have a distinct dissolving action on proteins, etc. In all the sites of fœtal invasion studied in the preceding pages I have pointed out the indisputable occurrence of some influence which arises in the chorion and which tends to throw the maternal tissues into a state of solution. This tissue change was most evident in the muscular elements, which invariably, in the neighbourhood of the fœtal cells in the pregnant tube and in chorionepithelioma, break up and disappear. Whilst most marked in the immediate proximity of the chorionic elements, the change is often evident at a long distance, a fact which proves conclusively that the crumbling away and ultimate disappearance is not due to a phagocytic action. The same dissolving activity of the chorionic cells on the maternal tissues has been described by Bryce and Teacher in the case of their ovum implanted in the uterine mucosa. It would also seem to be occurring in the necrotic zone in my specimen. In the account of their early specimen, Teacher and Bryce especially refer to the absence of any phagocytosis, and they advance the belief that the changes are probably dependent on some extracellular substances, perhaps of the nature of enzymes, liberated by the fœtal cells.

Laboratory research has demonstrated that the products of protein digestion have an osmotic tension greater than that of the substance from which they are derived, and it seems to me that in this fact we must look for an explanation of many of the phenomena which I have described on the preceding pages. In the degenerating muscle I have shown there are undoubted evidences of an increased attraction for fluid. Here the disintegrative process culminates in a solution of the muscular substance; in other words, there is a true digestion. This change is dependent on the especial susceptibility of this tissue to the chorionic influence. In the case of the endothelial and connective-tissue elements, on the other hand, the resistance offered is greater, and, for the most part, the protoplasmic changes do not advance beyond a splitting-up of the cytoplasm with an active imbibition of fluid by the cell, the nucleus of which usually retains its vitality throughout. Whilst this cellular change is widespread, and, in all the conditions described, results in an extensive passage of fluid and blood into the tissues, it does not necessarily

produce a dissolution of the cell. This is rare except where the endothelial or connective-tissue elements are strangled in the disintegrating muscle. I have pointed out that in the pregnant tube there is conclusive evidence of the fact that the protoplasmic alterations in the endothelial and connective-tissue cells lead in many cases to a more regular escape of the blood along newly formed tracks created by the confluence of the fluid spaces in the cells; in other words, that the process induced by the chorionic influence is, in these cases, no more degenerative in nature than is the formation of new blood-vessels. The explanation of the new formation is identical with that which accounts for the gradual and irregular dragging of the intravascular contents into more and more distant parts of the tubal wall, but in the former case the blood is drawn from the vessels along definite channels.

With regard to the mode of spread of the chorionic secretion the investigations recorded in the preceding pages furnish evidence of considerable importance. In the first place, the maternal changes are invariably most marked in the immediate proximity of the fœtal elements, and become less and less marked as the immediate site of their activity is left. The degree of involvement of the maternal structures is, for the most part, inversely proportional to the distance from the fœtal cells. This observation would seem to indicate that the biochemical substance extends its action by a process of diffusion. The effects of this diffusion are often marked at a long distance from the actual embryonic site. The only exception to this law is that the walls of the veins and the tissues adjoining them are often more involved in the degenerative process than the arterial walls and the tissues immediately surrounding them (*e.g.* pregnant tube). In this case there has occurred a transference along the vessels in the direction of the blood flow.

Changes in Mucosa before Imbedding of Ovum

The earliest stages of the changes which the maternal tissues exhibit in the human female are still uncertain. The earliest recognised ovum is about fourteen days old, and it is already completely imbedded in the mucosa. It is likely that the segmenting ovum lies free in the uterine cavity until the end of the first week. Whether or not during this time the mucosa remains unaltered, and that the first effect coincides with the epithelial destruction which immediately precedes the process of imbedding, must be a matter of conjecture, but some facts derived from a study of comparative embryology are suggestive in this connection.

In many animals definite structural changes in the mucosa are recognised whilst there is no attachment of the fœtal elements. By means of the activity of the mucosa the developing blastodermic vesicle is nourished whilst it is lying free in the uterine lumen, and in those cases where an interlocking of the fœtal and maternal tissues afterwards occurs the changes in the mucosa result in the preparation of a suitable bed for the ovum. I propose to refer in brief to a few of the animals in which the changes have been studied.*

In the rabbit, during the period when the blastodermic vesicle lies free (about eight days), there occur marked changes in the mucosa. As the result of a hyperplasia of the connective tissue and an increase in the number of blood-vessels there are produced the elevated pads on the placental folds to which the fœtal cells become eventually attached. Before this there occurs a marked œdematous infiltration of the superficial tissues. In the hedgehog somewhat similar changes occur. With the onset of pregnancy the anti-mesometrial folds of the mucosa become swollen, with a deepening of the fold in which the ovum develops. While it is still free there takes place a proliferation of the connective-tissue cells and an increase in the number of the blood-vessels. In places the vessels are distended. "These lumina are from the beginning so wide that they cannot be compared to ordinary capillaries, but must be looked upon as vascular formation *sui generis*" (Hubrecht). The lips of the furrow are intensely engorged, the tissues are infiltrated with an œdematous and blood escape, and hæmorrhages into the lumen occur. In the shrew, mole, and bat similar vascular and tissue changes are present before attachment takes place.

Whilst there is no doubt that the maternal changes to which I have referred are an index of the mucosa activity to supply nourishment to the ovum whilst it is free, and to prepare the subepithelial tissues for a ready flushing of the region of the ovum bed with a plentiful supply of nutriment after attaching, the changes with which we are specially concerned are even more evident in those animals where the developing ovum is free for a considerable period of pregnancy. In the pig, for example, attachment never occurs, and the ovum throughout pregnancy lies apposed to the mucosa, which is actively engaged in hurrying food to the surface levels. This is associated with an increase in the number and size of the blood-vessels, with a proliferation and expansion of the lymphatics, and with a marked infiltration of the superficial layers

* For a fuller description see *Physiology of Reproduction* (Marshall). Article on "Fœtal Nutrition," by Lochhead.

of the mucosa with lymph. At the same time there is an active glandular secretion in process, which leads to a marked expansion of the gland lumina. Similar changes are seen in the sheep and cow, where the blastodermic vesicles are free for a considerable time.

For long it has been recognised that these activities of the mucosa, whilst there is no intermingling of the fœtal and maternal elements, result in the elaboration of a definite food secretion or *uterine milk* for the nourishment of the developing ovum. In the ruminants this function is most in evidence, but there is no valid reason for doubting that a similar process is present in a less degree, and in proportion to the individual needs, in other animal orders. In the hedgehog, etc., the mucosa changes, in addition to adapting the subepithelial tissues for the reception of the ovum after imbedding, may indicate the preparation of an increased secretion which is poured into the lumen to nourish the young fœtus.

It seems to me that the investigations recorded on the preceding pages with regard to the mode of action of the fœtal elements supply us with a method of explaining many of these changes. We have seen that there is elaborated by the chorionic cells some material whose action is powerful, and the effect of which is often detected in the maternal tissues at a long distance from the actual location of the fœtal cells. It is especially suggestive to find that some of the most definite tissue changes which I have shown to be induced by this substance (œdema, increase in the number and size of the blood-vessels) are detected in the pregnant mucosa before imbedding. This coincidence, and the fact that these alterations are invariably most marked in the regions corresponding to the situation of the ovum, suggests strongly that this same extra-chorionic influence is acting again.

Whilst it would seem unlikely that the minute human ovum can exert before attachment anything more than a small influence on the tubal or uterine mucosa, it would seem highly probable that, when it comes to rest on the surface of the mucosa in the region corresponding to the site of imbedding, changes will be produced in the immediate tissues. The structural conformation of the mucosa would permit of a ready flushing of the subepithelial tissues with fluid and blood in response to the extrachorionic activity, and in this way a bed would be prepared in anticipation of imbedding. In view of what we have noted on previous pages, also, it is likely that when development arrives at the stage for imbedding the same influence will transform the substance of the

epithelial cells into soluble materials and thus provide the gap necessary for the entrance of the ovum.

Mode of Opening up of Maternal Vessels

I have shown in a previous chapter that the main characteristic of the vessels of the endometrium is that, by virtue of their peculiar structure, they are adapted, in a manner which must be considered to be perfect from the point of view of efficiency, to open up and discharge their contents into the adjoining part of the stroma. Almost immediately after reaching the endometrium the vessels, which extend from the muscular wall of the uterus, throw off their specialised supporting coats. Except in the very deepest region of the mucosa the walls of the vessels are completely devoid of elastic and muscular tissue, and are formed by the surrounding connective-tissue elements. Where necessary these are packed together to lend support to the vascular wall, but in such a way as to permit of their ready separation when the occasion should arise. The internal layer, also, is formed by cells which coincide in every respect with the stroma elements. As the result of the study of the vascular changes during menstruation I have shown that by a detachment and separation from one another, not only of the more external cells but also of the lining cells, there is allowed an immediate and free escape into the surrounding stroma of the contained fluid and corpuscles. In the ease with which these changes occur the consistence of the stroma plays an important part. We have seen that during menstruation the stroma must be considered to consist of a soft, semi-fluid material. This determines at once the facility with which the vascular walls become teased out, and the ease with which the liberated contents can pass into and displace the surrounding stroma. In this way only can we understand how there is created, especially round the glands and under the surface epithelium, the large fluid and blood areas which appear in the menstrual mucosa.

I have demonstrated in a preceding chapter that the cause of the fluid and blood escape into the tissues during menstruation is to be found in a diffuse protoplasmic change which determines an active imbibition of the intravascular contents. The leakage is more than a mechanical process due to a congestion. The protoplasmic mass of which the stroma is formed is clearly specially adapted for the exhibition of these changes. Throughout it is a potential blood sponge. The ready response of the stroma to the influence causing the menstrual process implies the

existence of a means by which any part may at any moment become suffused with the elements of the blood, fluid and corpuscles.

We may be sure that these structural peculiarities of the mucosa vessels and stroma are bound up with the changes which the maternal tissues exhibit after the imbedding of the ovum.

The changes which the vessels exhibit in the mucosa round the engrafted ovum may be tabulated as follows :—

(1) The cells forming the vascular walls become teased apart and the concentric layers of supporting cells found in the vessels of the resting state become stripped off from the lining layer in a manner identical in every respect with the process as it occurs in menstruation (Chapter II.). This has resulted, in Peters' specimen, in a complete disappearance of the thicker-walled vessels in the mucosa near the ovum. There is also apt to be a detachment of the endothelial cells and an opening out of the vessel wall. These changes I have also noted in my early ovum.

(2) These changes are associated with a marked œdematous infiltration and a hæmorrhagic escape into the stroma, the cells of which, except where they are packed together as the result of a decidual change, are spread apart and completely detached save for the presence of intervening processes of their protoplasm. Through the vessel walls the red blood corpuscles are often seen streaming into the adjacent tissues and towards the surface of the chorionic membrane. Where there has occurred a marked decidual change in the stroma elements the watery and corpuscular infiltration of the tissues is less marked, and the vessels, even in the immediate vicinity of the implantation cavity, are apparently well supported by the enlarged decidual cells (Bryce-Teacher ovum). These observations will be referred to again in the next chapter.

(3) There is, besides a loosening of the vessel walls and an œdematous and corpuscular escape into the tissues, a marked distension of the vessels throughout the mucosa adjoining the site of the ovum. This is present in all the early specimens, and is one of the most characteristic features seen. In Peters' specimen the distension of the vessels is associated with an advance of their walls towards the chorionic surface carrying in this way the contained blood to the region of the ovum. In many cases the expanding lumen is separated from

the fœtal surface only by the endothelial layer. In some cases, however, this may disappear. Round the walls of the expanding vessels there is a hæmorrhagic escape. These appearances I have referred to in my specimen.

The distension of the vessels results in the formation throughout the mucosa adjoining the ovum of large blood sinuses or lacunæ. These may be lined by a layer of flattened cells, or they may, in parts, be bounded apparently by the ordinary stroma cells.

(4) In Peters' specimen, in which there is less evidence of a necrotic change in the neighbouring structures than in any of the other early ova, there has occurred in the decidual tissue round the ovum a formation of new capillary vessels.

The fact that there is an opening up of the maternal vessels and an escape of the contents into the surrounding tissues beyond the regions of the actual chorionic invasion would seem without doubt to demonstrate that there is in operation in the production of the hæmorrhage something more than a direct invasion of the vessel walls and a mechanical liberation of the contained blood. The conditions present in Peters' specimen and in that which I have described warrant such a conclusion.

It will be seen from the above *résumé* of the conditions present in the case of the earliest described ova that the maternal changes coincide, in so far as the vascular alterations are concerned, almost exactly with those which I have recorded in connection with the pregnant tube and the chorionepitheliomatous uterus. We have seen how in both cases there is a well-marked œdematous and blood infiltration of the tissues, which, though most evident in the immediate vicinity of the fœtal elements, is still manifest at a distance from the actual site of the cellular invasion. We have seen, also, a marked vascular distension in both regions, which especially affects the vessels with thin walls, and we have, in addition, observed how, in advance of the chorionic line of attack, the vascular walls become opened out and the vessel virtually advances through the tissues towards the chorionic surface.

In the abnormal regions of chorionic activity the maternal changes can be explained only by recognising the existence of a biochemical material or materials which emanate from the fœtal cells and which spread further and further into the surrounding tissues. The colloidal constitution of these is so altered by this substance as to lead to a wide-

spread imbibition of the blood fluid and corpuscles. The opening out of the vessels is due to an œdematous teasing asunder of the confines in consequence of the active * tissue changes. These determine the escape of the vessel contents, which are dragged further and further into the adjoining tissues by the enhanced affinity for fluid of the colloids of the maternal structures. Indisputable evidence of an active imbibition is found in the alterations in the connective-tissue, endothelial, and muscular elements. The last named quickly exhibits a necrotic change, and this may be present even at a considerable distance from the fœtal cells.

As the uterine stroma and vessels are composed throughout of a soft, mobile, connective tissue which, as I have shown, is especially adapted for the exhibition of changes identical with those which occur in the connective-tissue elements of the pregnant tube, etc., it would seem more than likely that we are now provided with a means of explaining the maternal change in pregnancy. In the last chapter I have demonstrated the existence in the stroma round the early ovum of protoplasmic changes which have determined an active and widespread imbibition of the blood fluid. It is these changes which have determined the marked œdematous opening out of the tissues. The teasing apart of the vessel walls by the escaping fluid has been followed by a dragging of the blood into more and more distant parts of the mucosa. The maximum change, as one would expect, is found in the vicinity of the ovum. It might be argued that the discovery of such protoplasmic changes in a single specimen, especially in view of the manner in which that specimen was obtained, do not justify anything more than a very theoretical application. It must, however, I think be admitted that, taken in conjunction with the special structural conformation of the mucosa and the changes present during menstruation to which I have directed attention, and, in addition, the extensive investigations into the mode of action of the chorionic epithelium which have been given in preceding chapters, we are now provided with a key with which to unlock many of the secrets of the changes which the uterine mucosa undergoes during pregnancy.

The flushing of the mucosa in the proximity of the young ovum with the maternal blood is due to a widespread alteration in the chemical constitution of the stroma protoplasm which leads to an increased affinity for the blood fluid. This change is brought about by the extra-

* "Active" is here used merely in the sense of "not passive." Anything "vital" in the ordinary sense is not intended.

cellular materials elaborated by the ectodermic cells of the blastocyst, which first affect the immediately adjacent tissues, but which spread by a process of diffusion into more and more distant levels of the mucosa with the increase in the size of the ovum. This protoplasmic change in the earliest stages is evidenced at any part by an increase in the size of the intercellular spaces and by an accumulation in the cytoplasm of the stroma of fluid, which has been imbibed, and which is contained in many places within chambers walled in on every side by the displaced protoplasm. The breaking up of the protoplasm into fine films separating the fluid spaces accounts for the appearance of the fine so-called network in the stroma, the importance of which has already been described in Chapter II. This fluid transference from vessel to tissue leads to an opening out of the vessel walls. In the better supported vessels there occurs a stripping-off of the outer cells often in concentric layers, the change naturally occurring from without inwards, until ultimately the intimal elements are separated and there takes place a free escape of the red cells. These changes I have described in my specimen. They are well marked also in Peters' ovum. In the finer vessels (and we will remember that the majority of the mucosa vessels at the surface correspond merely to poorly supported capillary twigs) the teasing apart of the stroma permits of an immediate leakage of the blood. Such a leakage probably occurs at the surface levels even before the ovum is imbedded; after this has occurred it is easy to see how the chorionic influence will immediately provoke the marked œdematous and hæmorrhagic infiltration of the tissues present in all the early ova described. In the last chapter I have shown that the mucosa in a wide circle round the cavity of the young ovum is invariably the seat of a copious blood escape and that the red cells can be seen extending across the space intervening between the vessels and the blood chamber. In the necrotic zone large numbers of well-preserved red cells are present. The appearances all suggest that it is by a process such as I have described that the early ovum obtains its blood supply. In discussing the intrachorionic activity of the chorion I shall point out that in the initial stage, before a circulation of the maternal blood over the surface of the ovum has been properly established, there would seem to be the provision of a mechanism by which the ovum can actively pass the fluid and corpuscles on to the outer wall of the blastocyst.

Explanation of Formation of Sinuses in Pregnant Mucosa

It seems to me that, in addition to explaining the œdematous and

blood exodus, the tissue changes to which attention has been directed provide an explanation of the vascular expansion which is characteristically exhibited in the young decidua round the ovum, and they explain how in many cases the vessels come to open directly into the implantation chamber. In the pregnant tube and in the wall of the chorionepitheliomatous uterus we have seen that the large thin-walled blood spaces or sinuses which develop are not formed by a mere mechanical expansion in response to an increase in the intravascular tension. A careful scrutiny of the histological changes associated with the process indicated beyond doubt that the expansion is induced by changes identical with those which lead to the widespread œdematous opening out of the tissues. The factor responsible for the expansion of the vessel wall is similar to that which determines the displacement of the surrounding tissues. It consists in an active imbibition by the stroma of the vessel boundary. The disappearance of the fine protoplasmic film on the inner aspect carries the blood space a corresponding extent outwards. The continuance of this process of imbibition, followed by displacement, by the connective-tissue elements, which are successively encountered by the expanding vessel wall, results in a greater and greater increase in the lumen. The force causing this increase in size is not the hydrostatic pressure of the blood. It is to be measured by the increased affinity of the tissue colloids for fluid. I have shown that we have evidence of a similar process in operation in the expansion of the vessels into sinuses or "distended capillaries" which occurs in the menstrual mucosa. Here the expansion takes place with the greatest ease because of the soft nature of the stroma. The escaping fluid teases out the vessel wall in the manner represented on Plate III. I believe that the expanded vessels or sinuses encountered in the mucosa round the young ovum are formed in a way similar to the process as it is clearly recognised in the menstrual stroma and in the wall of the pregnant tube, etc. The protoplasmic changes induced by the chorionic materials will lead to an increasing expansion of the vessels. This change can occur at once in the finest vessels, and it can occur in the thicker vessels after the teasing asunder of the supporting stroma elements. As in the menstrual mucosa and the wall of the pregnant tube, the distension of the wall occurs at the expense of the surrounding connective-tissue elements, which are incorporated as a new lining. Sometimes this inner layer is flattened, at other times the cells differ in no respect from the surrounding stroma (see Chapter II.).

Cause of Opening of Vessels into Implantation Cavity

In the case of the vessels which lie near to the implantation chamber the invasion of the stroma by the expanding wall tends to bring the contained blood nearer and nearer the ovum. This process is well shown in the Peters specimen, and it is also evident in that which I have placed on record. It corresponds to the phenomena which I have described in the pregnant tube, and in the uterine wall in chorion-epithelioma, where *the vessel is seen to be opening out and virtually advancing through the tissues to meet the invading fœtal cells.* In the pregnant mucosa, as in these abnormal sites of fœtal activity, there is often present an escape of red cells into the tissues round the periphery of the distending vessel.

The extrachorionic influence is most pronounced in the immediate neighbourhood of the implantation chamber, and here the tissue and vessel changes are most marked. It is easy to see that the continual displacement of the stroma by the advancing vessel walls will eventually culminate, in the case of those vessels near the ovum, in an opening of the lumina into the implantation chamber. This process, I believe, explains the phenomena adequately, and it is unnecessary to invoke the presence of a mechanical giving way of the thinned-out vessel wall before the intravascular pressure, such as Peters has suggested. I have shown how in the pregnant tube the gaping of the vessels in the way above described is associated with a wholesale solution of the maternal elements nearest the fœtal cells. Teacher and Bryce have referred to a similar change in the marginal necrotic zone of the decidua, and at some places in my specimen there would seem to be a similar dissolving process in action. It has been supposed that this process accounts for the giving way of the vessel walls. From the description of the changes, however, which I have given above, it is clear that for a gaping of the maternal vessels a destruction or solution of their walls is unnecessary; in fact, the structure and consistence of the stroma and vessels are to be recognised as of such a kind as to allow of a *displacement* of the vessel boundaries and a wholesale blood escape with the greatest possible ease. The changes beyond the necrotic zone indicate that to explain the mode by which the vessels open into the ovum cavity we have to recognise the existence of a process other than a mere destruction of their walls with a mechanical outpouring of the blood. I shall refer again to the probable significance of the necrotic zone of the decidua.

The expansion of the vessels to form large, thin-walled blood sinuses, to which I have just referred, is one of the most characteristic conditions found in the pregnant mucosa. It is present normally in the human decidua. It is present also as a characteristic maternal change in the decidua throughout the animal kingdom. It has been noted by most observers, but it would seem that Hubrecht, in his account of the placentation of the hedgehog, was the first to recognise the peculiar nature of the change. In his work he says that these lumina are "so wide that they cannot be compared to ordinary capillaries, but must be looked upon as a vascular formation *sui generis*." * So far as I know their origin has never before been explained.

Formation of New Vessels in Young Decidua

Peters described the formation of new capillary vessels in the decidua round the young ovum. In many of my sections I have noted appearances suggestive of a new vessel formation. In Plate XX., which corresponds to a portion of the decidua at some little distance from the implantation chamber, spaces are seen which look like fine vessels cut in transverse section. In these spaces red cells may be detected. What is the significance of these appearances?

In an earlier chapter (Chapter III.) I have referred to the fact that in the pregnant tube one frequently detects the formation of new capillary channels leading from the original vessels into the surrounding tissues (Plate VII.). In that place I advanced observations in favour of the belief that this new formation is determined in response to exactly the same changes as lead to the marked irregular dragging out of the blood fluid and corpuscles from the vessels to form the œdema and hæmorrhage so characteristically found in the pregnant tube. These are dependent on a widespread change in the protoplasm of the endothelial, connective-tissue, and muscle cells, which endow them with the faculty of seizing an increased quantity of fluid. Where the fluid and blood are drawn into the tissues, not in such an irregular manner, but along a definite channel formed by a confluence of the intracellular fluid spaces produced in the endothelial and connective-tissue elements, we get the appearance of a new capillary vessel.

I believe that the capillary formation in the pregnant mucosa is subject to a similar explanation. In preceding chapters I have shown that the connective tissue of the endometrium is a protoplasmic mass

* *Journal of Micros. Science*, vol. xxx. "The Placentation of Erinaceus Europæus," p. 398.

which is especially constructed to allow a ready opening out of the fluid spaces which break up the tissue into small nucleated portions or undifferentiated "cells." These are to be considered, not as a series of spaces which freely communicate with their neighbours, but as chambers which are walled in on every side by the protoplasmic connections which extend between adjacent cells. These connections are not threads but fine sheets, and the stroma is enabled, by the presence of these films, which function as a colloidal membrane, to imbibe fluid from the blood-vessels in a manner somewhat similar to that which occurs during osmosis; a similar process breaks up the cell-protoplasm into fluid-containing chambers. The disappearance of the films throws adjacent spaces into continuity, and in this way comparatively large fluid-containing spaces are formed during menstruation and pregnancy. A similar process accounts for the gradually increasing blood sinuses formed in the pregnant mucosa.

It is clear that, if, instead of passing out round the vessel circumference as usually occurs, the fluid and blood escape along a channel formed by an amalgamation of adjacent spaces in the way described above, a fine capillary will be formed. This appearance is frequently detected in the mucosa during menstruation, and accounts, I believe, for the description given by many authors of a new vessel formation in this condition. Both in menstruation and in pregnancy the blood leakage from the vessels is usually found to be occurring more or less uniformly round the vessel circumference. The ease with which this takes place depends on the peculiar structural character of the mucosa. This consideration explains why, although the blood is being drawn into the tissues in response to the change which determines a new capillary formation, this is apt to be concealed.

Jung, in the description of his early ovum, has taken objection to Peters' interpretation of the appearances suggesting the existence of a new capillary formation. Jung states that the fine vessels described by Peters may in reality correspond to larger vessels which have been compressed, or they may correspond simply to intercellular spaces in which free red cells lie. It will be evident from the description given above why fine, newly-formed vessels and intercellular spaces containing blood cells are indistinguishable—in fact, in their mode of occurrence the two conditions are essentially the same.

Changes in the Muscular Wall of the Pregnant Uterus

As I shall show, in the next chapter, the process by which there

occur the vessel and tissue changes to which I have referred is quickly obscured by the decidual transformation of the stroma elements. After a short time there is left little or no indication of the manner in which the mucosa vessels have opened into the implantation cavity or have expanded into sinuses. The changes would seem to become less and less evident with the development of the decidua, and when this has reached its zenith they cease altogether in the mucosa. The importance of these observations with regard to the function of the decidua will be emphasised in the next chapter; in the meantime I want to refer to the fact that, even after the vascular changes in the mucosa in response to the chorionic influence have come to an end, one can often detect alterations identical with those which I have described in the muscular wall of the uterus (Figs. 61 and 66). These I have noted as late as the sixth month of pregnancy. In this region there does not occur under normal circumstances the irregular œdematous and hæmorrhagic escape from the vessels such as occur in the young decidua. This I believe is dependent on the fact that the tissue alterations are localised by the presence of the muscular bundles, which undergo a progressive hypertrophy. I believe that it is probable that the blood sinuses which develop so characteristically in the muscular wall of the pregnant uterus are formed in a way similar to that which accounts for their appearance in the mucosa and in the pregnant tube. They are formed, in other words, not by a mechanical expansion but in response to the tissue changes which I have described. As in the pregnant tube, they often exhibit a very irregular contour. Their shape and size are in many cases obviously determined by the muscular bundles, whose presence serves to prevent the expansion from becoming excessive.

In the above paragraphs it has been shown that the complex of tissue changes which characterise the early pregnant mucosa reduces itself to a maternal reaction by which the blood—fluid and cells—is drawn from the vessels into the surrounding tissues and towards the implantation chamber for the nutrition of the young ovum. In the initial stages the fluid constituent of the blood is that involved in the process. This is determined by the nature of the tissue changes which the chorionic substances induce, and it clearly explains the well-marked œdema which characterises the maternal tissues round the ovum. The escape of the red cells follows in the wake of this watery infiltration of the tissues.

Up to the present I have, in describing the changes, referred to the fact that the alterations in the maternal protoplasm are to be considered

as without doubt leading to an enhanced affinity for the watery element of the blood, and the histological appearances would seem to warrant the conclusion that the materials in solution do not pass out of the vessels except when a complete teasing out has taken place. Whether or not this is actually the whole truth it is impossible to state with certainty. The fact that in the fluid spaces formed in the stroma protoplasm as the result of an active imbibition one can often detect a sort of coagulum or precipitate would suggest that there is more than a mere transmission of water taking place. This solid matter in solution may be derived from the blood or it may originate from the cell protoplasm. In this connection it is suggestive to remember that in many of the lower animals the extrachorionic influence calls into existence a secretory activity on the part of the mucosa with the elaboration of a milk-like material which is passed into the uterine lumen and which is absorbed by the ovum. In this case there exists, between the maternal blood and the ovum, an epithelial surface without which it is conceivable a true secretion may be impossible. Be this as it may, it is not unlikely that future research will reveal the fact that the maternal changes which I have described are associated with a transmission of the nourishing elements of the blood fluid before a complete opening up of the vessels and stroma occurs.

Several authors have described a mitotic division of the stroma cells round the ovum. The exact explanation of this it is difficult to give. It may be associated with the performance of the functions described above. As has been frequently pointed out, also, it is in all probability intimately bound up with the formation of a decidual membrane. This point I shall refer to in the following chapter.

Mode of Formation of the Implantation Cavity

On a previous page I have referred to the likelihood of the extra-chorionic influence calling into existence the maternal changes which characterise the reaction of the stroma to the extracellular substances immediately the ovum settles on the surface of the mucosa at the spot selected for the imbedding process, and even before any epithelial destruction has taken place. This is a conclusion to which we are driven by an investigation of the mode of action of the substances liberated by the chorionic cells and the recognition of the fact that these speedily diffuse into the maternal tissues. If this conclusion be correct there will take place an œdematous and hæmorrhagic opening

out of the stroma at the surface of the mucosa immediately under the ovum, corresponding to a kind of localised exhibition of the changes which occur in the premenstrual phase, when there are produced small blood-containing cavities under the surface epithelium. As I have previously indicated, the enlarging ovum will grow into this blood-containing space immediately after the removal of the few epithelial cells necessary for imbedding. With the increase in the blastocyst there will occur a gradual expansion of this blood space from a minute size up to the dimensions of the implantation chamber as it is first recognised in the several described specimens of early ova.

These considerations thus suggest that the ovum cavity has its origin in a displacement of the stroma similar to that which results in an opening out of the vessel walls, and which in many places leads to an expansion of the vessels to form blood sinuses. The process is likewise identical with that which produces an œdematous and blood infiltration throughout the stroma round the implantation chamber. It would seem unlikely, in view of the consistency of physiological processes, that one arrangement should be set aside for the expansion of the blood-vessels, an expansion which in some cases may be immense and may result in the formation of a blood space in the decidual mucosa almost as large as the ovum cavity (*e.g.* Peters' specimen), and that a quite different arrangement should be necessary for the formation of this cavity.

The process which I have described to account for the formation of the implantation chamber finds a close analogy in the manner in which the part of a vessel containing a villus in the pregnant tube or a mass of fœtal cells in chorionepithelioma is often seen to expand in an aneurismal fashion. This appearance I have noted in detail in preceding chapters. Teacher, who first pointed to this suggestive analogy, believed that the vascular expansion was determined by a disintegrative change in the wall induced by the fœtal cells which allowed of a mechanical opening out. I have elsewhere shown that in many cases it is evident that the expansion of the vessels is determined in response to the tissue changes which lead to an active fluid imbibition, and in cases where the disintegrative change to which Teacher refers is either absent or is only slightly marked.

These facts would suggest that the well-marked marginal necrotic zone encountered in several of the early ova is to be considered more as an incident than as indicating that the implantation chamber is formed by a destruction and erosion or solution of the mucosa *en masse*. Whilst

this is so, there can be little doubt that a number of the gland tubules in the affected area must degenerate and disappear.

It has been suggested that the blood shed into the ovum cavity from the opened maternal vessels may help to stretch the soft necrotic tissue and in this way aid in the expansion. It seems to me unlikely that a mechanical process of this nature can be in operation, for if the tension were great enough to accomplish this it could not fail to split the roof of the chamber, which in several cases, *e.g.* Peters' specimen, is very poorly supported. The explanation which I have advanced possesses the advantage of indicating how the blood cavity can become progressively larger without any marked increase in the blood tension. The blood, as it were, burrows outwards further and further between the stroma cells as the result of the local fluid imbibition and displacement occurring round the cavity. It seems likely that the blood tension at this time is so small as to be insufficient to allow of an adequate circulation over the surface of the blastocyst.

The development of the ovum in its cavity is associated with a marked swelling of the mucosa which, at the part, is elevated as a "decidual lobule." This swelling is produced as the result of the tissue changes to which I have referred; it is probably also partly due to the active proliferation of the stroma elements.

In some of the lower animals the ovum induces a marked necrotic change in, followed by a solution of, the immediate maternal tissues. In some, *e.g.* the guinea-pig, there is present a change which suggests that the cavity which is prepared for the reception of the ovum is formed in a manner somewhat similar to that which I have advanced for the human. In the guinea-pig the blood space would seem to be enlarging by the formation in the degenerating tissue or symplasma of clear spaces or "vacuoles" which increase in size, coalesce, and replace the necrosed material (v. Spee).* In view of what I have said on previous pages, it would seem not unlikely that in this change we have an indication of tissue alterations which lead to a dragging first of the blood fluid and then of the red cells towards the chorionic surface. As in the human, it is probably this change and not a direct excavation by the invading fœtal cells which results in the production of the blood-containing space. Into this the ovum *subsequently* grows.

The Intrachorionic Action of the Fœtal Ectoderm

For long it was believed that the fluid and the soluble ingredients

* *Zeitschr. f. Morph. u. Anthropol.*, Band iii., 1901, Tafel viii.

necessary for the nourishment of the ovum passed across the fœtal epithelium from the mother's blood by a proeess of diffusion or osmosis. In the light of recent research it would seem likely that the process is more complicated, and that the transference, at any rate of many of the nutritional elements, is dependent on an activity of the chorionic cells which may possess the funetion of transforming some of the food-stuffs taken up from the maternal blood into a state suitable for assimilation by the cells of the blastocyst and the embryo. For an account of these processes I would refer the reader to the various monographs on the subject.*

In this plaee I wish to refer to some histologieal appearances which have a possible bearing on the manner in which the blastocyst acquires its food supply in the earliest stages of its development.

Whilst the process which I have deseribed in previons sections of this work explains how the mueosa in the proximity of, and for some distance from, the ovum beeomes flushed with the blood fluid and the blood eells, and whilst it readily aecounts for an opening out of the nearer of the vessels into the implantation chamber, it does not imply the establishment of a free and liberal *circulation* of blood into the eavity. In fact, the very nature of the proeess, and espeeially the observation that the blood-vessels running towards the ovum must in the earliest stages be subjected to a continual depletion of their contents, which are being drawn into the tissues in response to the protoplasmic changes, suggest that a very inefficient passage of blood will take plaee for a certain interval towards the region where it is most required.

It seems to me not unlikely that it is for the purpose of bridging over this interval that the surfaee of the early blastocyst is provided with an arrangement by whieh it ean aetively draw towards itself a liberal quantity of the blood fluid and cells, whieh are essential to its growth. In their early ovum Teacher and Bryee have described a remarkable structural feature in the shape of a thiek plasmodial eovering which is broken up by spaces of greatly varying size into a complicated retienlar arrangement. They state that "the whole appearances presented by the plasmodium lead one to infer that the extraordinary irregularity in the disposition of the layer is due to a proeess of vaeuolation which has broken up the larger solid masses into a sponge-work, and that the trabeeulæ of this sponge-work have broken down so as to allow the blood shed into the implantation space by the opening of the

* See Marshall's *Physiology of Reproduction*, 1910; article on "Fœtal Nutrition" by Lochhead.

vessels to pass into the meshes. We thus reach a conception of the origin of the primitive blood lacunæ in the trophoblast not unlike that of Peters, but it will be observed that the spaces are produced, in the first instance, entirely in the plasmodi-trophoblast."

The spaces formed in the plasmodium are at first apparently empty or are occupied by a granular sort of material. Later they contain maternal blood cells, and there can be little doubt that the spaces are formed as Teacher and Bryce have indicated, for the purpose of providing lacunæ into which the mother's blood is received. After the investigations, which I have recorded in previous paragraphs, a suggestive analogy will be noted between the changes which the plasmodium is undergoing in this early ovum and the maternal changes, the object of which is clearly to allow of an active transmission of the blood from the vessels into the surrounding regions. As in the stroma of the uterine mucosa, where there occurs a collection of fluid in spaces in the protoplasm that subsequently receive the red cells, so in the plasmodium the vacuolation results in the formation of clear spaces which become connected with the maternal blood cavity and become occupied with the mother's blood.

In view of these considerations I would venture to assert that the thick plasmodium with which the blastocyst is provided at this early stage of its development is for the purpose of determining an active drawing of the nourishing maternal fluid in as great a quantity as possible towards the surface of the blastocyst. The clear spaces correspond to the maternal fluid which is passing into the plasmodial substance by a process of "imbibition" similar to the process as I have described it in previous chapters, and indicate in a visible way the manner in which the fluid, which the rapidly proliferating fœtal cells demand, is passing from the maternal blood space to the ovum. With a giving way of the films, to which the plasmodial substance is reduced by the increasing expansion of the fluid-containing chambers, the undiluted mother's blood gains access. By a continuation of this process, which must operate from without inwards (and it is suggestive to find that the largest spaces correspond to the outer aspect of the plasmodium), the blastocyst is bathed round its entire circumference with the maternal blood.

The truth of this conception of the function of the early plasmodium is confirmed by remembering that the extraordinary development of this soft displaceable material coincides with the interval when it seems unlikely that the stroma changes of themselves are still unable to

establish an active circulation of the maternal fluid towards the blastocyst. When, at a later stage, a more active fluid stream is obtained, this intricate plasmodial structure is unnecessary and it disappears. It is absent in the Peters and Jung ova and in the specimen which I have described. The speedy disappearance of the greater part of the plasmodium suggests that it enters into a state of solution, and it is by this process, in all probability, that the breaking down of the tissue strands separating the fluid chambers occurs. In this respect, again, we have an analogy with what probably occurs, at any rate in part, in the stroma of the mucosa.

It has for long been recognised that the plasmodium, even at comparatively late stages of development, is liable to exhibit a vacuolation of its substance, and that into the spaces thus formed the maternal blood cells pass, and it is likely that here again we have an indication of the same process as I have described above, though on a greatly reduced scale. The condition is frequently observed in the pregnant tube and in chorionepithelioma.

Structural changes similar to those presented by the plasmodium are sometimes detected in the Langhans' cellular layer of the trophoblast. They have been described by Peters in his early ovum.

Changes similar to those just described have been recognised by Hubrecht in the hedgehog and shrew, by v. Beneden in the bat, and by Duval in several of the rodents. It therefore seems likely that the process as I have interpreted it is widely spread throughout the animal kingdom as a mechanism by which the intimate relationship between the surface of the blastocyst and the maternal blood is accomplished.

Cause of Softening of Cervix and Vagina, and of the Extra-genital Œdema of Pregnancy

During pregnancy there occurs a marked softening of the cervix uteri and of the vagina. This condition commences early, and it becomes more and more marked as pregnancy increases. It permits an easy opening up of the maternal soft parts during the first and second stages of labour. From a histological examination of the tissues I am led to believe that the cause is to be found in protoplasmic changes similar to those which I have described in the maternal tissues in the pregnant tube, in chorionepithelioma, and in the mucosa and muscular wall of the uterus during a normal pregnancy. The softening is dependent on a soddening of the regions concerned with fluid which has been

sucked into the tissues in consequence of an alteration in the colloids, which increases their affinity for fluid. In view of what has been said on previous pages, there can be little doubt that this change is determined by the substances spreading from the chorionic cells. The distance of the tissues involved from the site of the ovum would seem to warrant the conclusion that the chorionic influence has reached them *via* the blood-stream.

It is well known that during pregnancy there is apt to occur a widespread œdematous swelling of the tissues throughout the body. This condition is more prone to occur in some women than in others. It is especially apt to develop in the lower and upper limbs, and the degree in which it is exhibited often arouses the suspicion of an involvement of the kidneys. In many cases, however, even where the wrists and fingers are markedly swollen, an examination of the urine reveals a healthy state of the kidneys. The fact that the upper limbs are not infrequently affected disproves the idea that the subcutaneous œdema, which develops so frequently and so characteristically during pregnancy, is dependent on a pressure on the veins, with a congestion and mechanical transudation of fluid—an explanation which otherwise might have accounted for the condition as encountered in the lower limbs.

The fact that we have been able to discover that the chorionic cells elaborate a material or materials that have the faculty of so transforming the protoplasm of the maternal tissues, and this even at a considerable distance from the fœtus, as to enhance its affinity for fluid, would suggest that in this we are provided with a clue to the *modus operandi* in these more generalised œdemas. In the light of the investigations recorded on previous pages it would seem not unlikely that by a passage of the chorionic materials into the blood there would be called into existence a widespread involvement of the body cells of the mother. This factor, also, may have a part to play in the better general nutrition often exhibited during pregnancy—it is well known that at this period the woman often experiences an improvement in health. The improved nutrition is often associated with a general increase in subcutaneous fat. It may well be that the increased fluid passage from the blood-vessels into the tissues implied by the chorionic stimulus carries the increased nutriment to the tissues.

It has for long been recognised that the mammary changes associated with pregnancy may be dependent on chemical substances reaching the glands from the placenta *via* the blood-stream. It is interesting in this connection to recall the fact that the enlargement of the breasts is

associated with an active proliferation of the glandular cells. A study of the changes in the uterine stroma during pregnancy would indicate that from the earliest period and with the formation of the decidua there occurs an active multiplication of the cellular elements, apparently in response to the chorionic stimulus. This point I shall touch on in next chapter.

In addition to the œdematous infiltration of the tissues which is found so characteristically in pregnancy there may actually occur a hæmorrhagic escape from the vessels in distant regions of the body, *e.g.* throat, gums, kidney.

CHAPTER VII

THE STRUCTURE AND FUNCTION OF THE DECIDUA

In this chapter I propose to discuss the decidua under two headings:—

(1) The Sites and Histological Characters of the Decidual Changes Detected in the Course of these Investigations, and

(2) The Function of the Decidual Membrane.

DECIDUAL CHANGES IN THE PREGNANT TUBE

In the wall of the pregnant tube a decidual change is found in the connective-tissue elements and in the endothelium.

Decidual Changes in the Connective-Tissue Cells

(1) Throughout the tubal wall there is apt to be an enlargement of the *intermuscular connective-tissue* elements in a manner similar to that which occurs in the uterine mucosa. This condition is, for the most part, most evident in the proximity of the fœtal cells. In this respect my specimens conform with those described by many previous workers on the subject. I have repeatedly, during the course of this record, referred to the existence of a vacuolated condition of the connective-tissue cells scattered throughout the wall of the pregnant tube. This change is much more manifest than the decidua-like enlargement. The former change is not infrequently associated with an extreme enlargement of the cell body, but it is due, not to an increase in cell substance, but to an accumulation of clear fluid. That the two different changes are dependent on the same common factor is suggested by the fact that in one place the decidual alteration is present, whilst in the vicinity the fluid distension is present. Each of the two conditions is traceable in the beginning to the chorionic influence, which in the one case determines an imbibition of fluid which collects in the cell, apparently unchanged, whilst in the other case it is coagulated or is built up into the cell substance. In each condition the nuclear changes are identical, namely a swelling and a deficient staining reaction.

(2) The region of the tube where the decidual change is found in the most marked degree is the *connective tissue of the mucous folds.* In one of the specimens (3 months) the condition is present in the folds throughout the entire extent of the tube, from fimbriæ to divided uterine end, except in the portion of the tube corresponding to the site of the gestation sac (the ampulla), where the mucous rugæ are, for the most part, detached. The decidual transformation of the connective-tissue cells is most evident towards the free surface of the folds, which have become enormously expanded in the process. The cells exhibit a marked enlargement of the cell body, which is granular in appearance. The nucleus is also increased in size, but not to the same extent as the cell body. The cells are closely packed together and are mostly rounded or polygonal in shape. A glance at Fig. 32 and Plate IX. will demonstrate that the resulting appearances coincide in every respect with what is encountered in the compact layer of the uterine decidua.

The perfect similarity between the decidual changes, which occur in the mucous rugæ of the tube, and those existing in the mucosa of the pregnant uterus, is clearly dependent on the like nature of the tissue present in these two different sites. In both regions it is represented by a connective tissue of a low type.

In all my other specimens a decidual change in the tubal mucosa to the extent found in this case is absent. That this difference is not dependent on the age of the embryo is proved by finding that, not only is the change poorly marked in the rugæ of the specimens corresponding to younger pregnancies than this, but it is almost entirely absent in the oldest specimens of the series.

From the point of view of one of the objects for which these investigations were made, namely an attempt to discover the functions of the normal decidual membrane, it is important to note that, with an exception to be recorded immediately, the only region of the tubal wall which has come under the fœtal influence and which is not ploughed up by an œdematous infiltrate, and in which the vascular walls are so well supported as to prevent a hæmorrhagic escape and an increasing distension of their lumina, is the subepithelial decidual tissue of the mucous rugæ. These changes are present to an excessive degree throughout the muscular wall of the entire series of pregnant tubes, and they are detected, in addition, in the mucous folds of those specimens in which the decidual enlargement of the cells is partially or wholly absent (Fig. 34).

(3) In many of my sections there is present a decidua-like enlarge-

ment of the *cells of the vessel walls,* where these are equipped with a muscular and connective-tissue coat. In these cases the decidual elements often form a layer several cells deep; in some instances the decidual change has led to a bulging of the inner part of the wall into the lumen, which may be considerably narrowed in the process. The decidual layer is often seen to be external to an unaltered endothelium (Fig. 37). This vascular change is often present at a considerable distance from the fœtal elements. The cells are easily recognised from those of the Langhans' layer of the chorion by the smaller size of the nuclei and by the fact that, in their neighbourhood, the maternal tissues are well preserved, a condition never found in the proximity of the embryonic cells.

Changes in the vessel walls similar to those just described have been previously observed by other authors (Hitschmann, Fellner, Kroemer, Schambacher, von Franqué and Garkisch, etc.). I refer to their occurrence in my specimens only for the purpose of describing their importance from an aspect which has hitherto escaped notice, namely that, whereas even in thick-walled vessels, in which these alterations are absent, there is apt to be a wholesale ploughing up of the walls by a fluid and blood exudation, in these cases this process is resisted, in some instances in a manner which is perfect.

Decidual Changes in the Endothelium

In my specimens of the pregnant tube decidual changes in the endothelial cells are present in two different sites—in the vessel lining and in the peritoneum.

(1) *Decidual Changes in the Vessel Endothelium*

In all my specimens there are found marked changes in the vascular endothelium. The most manifest is a vacuolation of the cell body. The structural alterations associated with this and its importance I have already referred to in a preceding section. Another endothelial change which has been described by a few observers is also sometimes noted, namely a proliferation of the nuclei and an increase in cell substance associated with the disappearance of the cellular outlines, with the production of a syncytium-like mass. That it is not due to a portion of syncytium deported from the fœtal area is proved by tracing the vessel in series.

In other regions of the affected tubes one notes, in addition to a

proliferative change, an enlargement of the cell bodies, in some cases occurring to the extent of identifying the cells with those found in the uterine decidua. In Fig. 36 is shown a vessel thus affected. Attached to the inner wall and sprouting into the vessel lumen is seen a mass of large cells, some of which are detached. This appearance I had several times noted in my specimens and had thought to be due to an extension along the vessel lumen of fœtal cells, which were in the process of invading the vessel wall. A subsequent study of the specimens has, however, convinced me that they, in reality, correspond to enlarged and proliferated endothelial cells. In the first place they are present often at a considerable distance from the ovum. In the second place it will be noted that there is no invasion of the vessel wall. The cells can be seen springing from the endothelial layer. In the third place they differ widely in structure from the chorionic cells—whilst the cell-body is much larger than the cells of Langhans' layer, the nucleus is smaller. Another fact of some importance is seen in the absence, in the groups, of syncytial buds. They correspond, in other words, to endothelial cells which have undergone marked proliferation, the newly-formed cells enlarging in a decidua-like manner. In other regions there would seem to be a decidual enlargement of the endothelial elements without a co-existing proliferation.

(2) *Decidual Changes in the Peritoneal Endothelium*

In two of my pregnant tubes I have detected a marked enlargement of the cells of the peritoneal covering. The detection of the change in this site is important in view of the fact that there is a vagueness in the literature regarding the possibility of its occurrence. I refer to it more especially in this place to emphasise a fact of considerable importance in connection with this research, namely the close resemblance existing between the endothelial and the connective-tissue cells in their mode of reaction to the presence of the fœtal elements.

I have already elsewhere described a decidua-like enlargement of the peritoneal endothelium as found in one of my specimens (3 months' pregnancy *). In this case the peritoneal covering had disappeared in most places; where present it was found to exhibit the change. Since recording this specimen I have had the opportunity of studying another, in which the change is much more evident. The age of this specimen

* "Anatomy and Histology of the Pregnant Tube," *Trans. Edin. Obstet. Soc.*, 1908-9.

was impossible to determine because of the fact that the fœtal remains were broken up by hæmorrhage. The appearances present suggest that it must have corresponded to a very early pregnancy, in all probability situated in an accessory ostium in the upper aspect of the tube. The remains of such a structure are distinctly discernible incorporated with the tubal wall and are found to encircle the fœtal remains. The probability of the pregnancy being of this nature is corroborated by the existence of a distinct accessory ostium in the opposite tube, which was removed at the same time.

Round a large part of the circumference of the specimen under discussion the peritoneal endothelium is well retained. The cells are everywhere enlarged, sometimes to a marked degree, and here again the increase in size has involved the cell-body to a greater degree than the nucleus—the characteristic change in the ordinary decidual cell of the pregnant uterus. The cell substance is distinctly granular as in the typical decidual cell. As in their swelling the cells have been closely packed together they have assumed a cubical or a columnar shape, and the surface of the tube thus appears as if covered by a continuous epithelium (Figs. 38 and 39). In many places the change is associated with a rugosity of the tubal surface. This is due partly to the existence of distinct villous protuberances, and partly to the fact that the swollen endothelial cells have dipped down into the superficial part of the tubal wall. The papillary projections sometimes attain a considerable size, and may here and there be seen cut across transversely, and appear to be lying free.

That these appearances are not due merely to a warping of the surface by the increase in the endothelial area in consequence of the swelling of the individual cells is proved by the existence of distinct evidence of a cellular proliferation. In many places the cells are seen to be several layers deep. The changes present, then, are to be attributed to two distinct factors—an increase in the size and an active proliferation of the cells. The cellular enlargement would seem without doubt to correspond to the decidual increase in size of the uterine stroma cells during pregnancy.

A study of the changes which the endothelial and the connective-tissue cells of the tubal wall exhibit in response to the influence of the engrafted ovum has demonstrated that in respect of the two important cellular alterations induced the two classes of cells coincide. In each type of cell there may occur a vacuolation of the cell substance due to an active fluid imbibition, or there may be a great increase in size

similar to what occurs in the pregnant uterus. I have suggested on a previous page that it is probable that these two changes, so different in their results, may in their origin correspond to the same common factor. In the one case the fluid imbibed has accumulated in the cell unchanged, in the other it may contain albuminous matter which is precipitated or is built up into the cell body. Be this as it may, it would seem that the complete similarity of the results, in each case dependent on the fœtal influence, is strong evidence in support of the conception that the two classes of cell are structurally alike. This idea is, as I have shown, confirmed by the finding that the connective-tissue elements may take part in the formation of a new endothelium.

DECIDUAL CHANGES IN UTERINE WALL IN CASE OF PLACENTAL RETENTION

In the specimen, in which I have been able to study the changes induced in the uterine wall by the influence of placental fragments which have been retained, a well-marked decidual reaction is present. This is evident in a portion of the mucosa adjacent to the villi. Most of this structure has disappeared in the specimen, and the villi come close up to the muscular wall. In no place was there an actual invasion of the muscle.

There is a well-marked enlargement of many of the intermuscular connective-tissue cells. The cell body, here again, is involved in the increase more than the nucleus. In some instances the altered cells are found in clumps, in other places they lie imbedded singly in the muscular bundles. The cells are indistinguishable in size and structure from the ordinary decidual cell.

In this specimen, as in the pregnant tube, the appearances favour the conception that the process which has determined the dropsical accumulation in the connective-tissue cells is to be identified with that which in other cases causes a decidual increase. Here again, in the same small area of the muscular tissue, cells exhibiting the former change are found close to cells exhibiting the latter. In many places, also, the muscle fibres are seen to be separated by clear spaces which with a low-power lens look like decidual cells, but which under higher magnification are seen to be unoccupied by a definite cellular material. In many of these spaces nuclei are lying, and the appearances seem to be due to intermuscular connective-tissue cells which have been the seat of a fluid distension.

In many regions of the muscular wall there are large multi-nucleated cells similar to those found in the decidua serotina. The fact that these are found scattered irregularly through the muscle, and often between the muscular bundles at a distance from the sites of the villous attachments, lends favour to the conception that they are maternal in origin. Such would seem also to be the most recent interpretation of the similar multinucleated cell masses seen in the serotina in normal pregnancy.

Another observation of considerable importance from the point of view of the decidual formation in this condition is seen in the fact that whereas in the uterine wall, even at a distance from the chorionic cells, there may be a marked hæmorrhagic escape from the vessels, where these are unsupported by a definite decidual change in the surrounding tissue, in the proximity of the fœtal cells, this alteration in the neighbouring connective-tissue elements seems to protect the vessels against the blood escape.

DECIDUAL CHANGES IN CHORIONEPITHELIOMATOUS UTERUS

The Endometrium

The changes in the uterine mucosa in chorionepithelioma differ in different cases.

The stroma cells not infrequently exhibit changes similar to those which I have described in connection with the menstrual process (Plates III. and IV.) and in the mucosa round the young ovum (Plate XIX.). As in these conditions, this is to be traced to an alteration in the tissue protoplasm which has determined a widespread "imbibition" of the blood fluid. It results in the appearance of the fine so-called tissue network, the explanation and importance of which I have described in full in previous chapters. As in the menstrual and pregnant conditions, these alterations are associated with a dragging of the red cells from the vessels into the stroma, and with the formation of the "distended capillaries" which appear so characteristically in menstruation and pregnancy. These changes in the mucosa are marked even at a considerable distance from the chorionic masses. Where the chorionic cells are infiltrating the mucosa the changes to which I have referred clearly constitute the manner in which the blood necessary for their growth is obtained.

In other cases the stroma cells of the mucosa undergo a true decidual

change. This was present in parts in two of my specimens. A point of considerable importance in connection with the function which the decidua subserves is found in the fact that with the enlargement of the stroma cells the fluid and hæmorrhagic escape from the vessels is absent. Moreover, at these regions the advance of the chorionic masses is clearly arrested. These findings I shall refer to more particularly in a subsequent section.

The Muscular Wall

Throughout the muscular coat the connective-tissue cells exhibit the decidual change to a well-marked degree (Fig. 53). The cells are in most cases easily distinguished from the fœtal cells with which they may be intermingled by the larger size of the cell body and the smaller size of the nucleus. In some places it is more difficult to determine with accuracy the origin of the cellular elements; this is especially true in the maternal tissue immediately adjacent to a clump of the fœtal cells. In all cases where there was the least difficulty in recognition I have, for the purpose of meeting critical objections, in describing the manner in which the blood escapes from the vessels, assumed that the doubtful cells were fœtal in origin.

The decidual cells are in some places closely set together to form masses of considerable size, in other cases they are found singly in the muscle bundles. In most places the nuclei are small and the cell body takes on a faint stain. In some instances, however, the nuclei may be large, even bigger than those of the Langhans' cells. That these correspond to maternal cells is indicated by their site: they are scattered about irregularly in the muscular tissue, and often at a considerable distance from the regions of the tumour masses. Two observations which prove their identity without doubt are the fact that the cell body is much larger than that of even the largest fœtal cells, and the fact that in their proximity the muscular tissue is not disintegrated to the extent invariably present in the neighbourhood of the chorionic cells. Here again it is interesting to note that where the change has occurred the œdematous ploughing up of the tissues which is present in other regions is absent. Even in the neighbourhood of the fœtal cells, also, the decidual enlargement of the connective-tissue cells has prevented the teasing asunder of, and the hæmorrhagic escape from, the maternal vessels. In the uterine wall there is the same dropsical distension of the cells which we have noted in the other regions of chorionic activity. The fact that the two changes exhibited by the connective-tissue

elements, namely a decidual enlargement and a fluid imbibition, are somewhat similar in their nature, though differing in their results, is suggested by finding the two cellular alterations side by side in the same small area of the uterine wall. In each case the change is associated with a swelling of the cell body, and in each case it is obvious that the condition is due to the same influence, namely a protoplasmic change induced by the chorionic activity. In one point there is a difference between the two kinds of structural change produced in the cells by the process causing an increase in the size. Whereas in the decidual cell the nucleus is more or less centrally placed, in the cell, the seat of a fluid imbibition, the nucleus is usually pushed to the periphery of the cell body, where it may be markedly flattened.

In the uterine wall there are detected large multinucleated cells similar to those present in the decidua serotina in normal pregnancy, and identical with those scattered irregularly about the uterine muscle in the specimen exhibiting the effects of placental remains. Here again I believe their origin from maternal connective-tissue cells is likely.

THE DECIDUAL MEMBRANE OF NORMAL PREGNANCY

This structure, as is well known, is composed of the mucous membrane, which during pregnancy becomes greatly thickened throughout the entire extent of the uterine body. The change, except in very rare instances, ceases at the level of the internal os. The increase is due almost entirely to the changes in the stroma elements. These become markedly enlarged to form the decidual cells. This change is most marked in the outermost region of the mucosa, which becomes the compacta. Here the main substance consists of the altered cells and the blood-vessels. There are few or no gland remains. In the deeper part of the mucosa there is a marked glandular hyperplasia and dilatation, transforming this region into the decidua spongiosa. In the tissue bridges between the expanded glands the alteration in the stroma cells is usually less marked than in the compact layer.

The decidua reflexa is the part of the uterine mucosa which intervenes between the implantation cavity and the uterine lumen. The decidua serotina separates the fœtus from the muscular wall of the uterus, and from it the maternal part of the placenta is formed. The decidua vera corresponds to the part of the altered mucosa not in direct relation with the fœtal structures. It forms, in the early months, the main part of the decidual membrane, and consists of that portion

of the thickened mucous membrane not comprised within the former two. Without touching on many of the aspects of the decidual membrane, which are described in the text-books on obstetrics, I shall pass on to consider it from the points of view which more particularly concern this investigation. I wish to approach the discussion of the subject under three headings:—

(1) The factors responsible for the decidual change.
(2) The structure of the decidual membrane.
(3) The function of the decidual membrane.

FACTORS RESPONSIBLE FOR DECIDUAL FORMATION

The exact stages in the process of the decidual alteration of the uterine mucosa are still incompletely filled in. Of some points, however, we may be certain. In Peters' early ovum the distinct decidual change is located entirely to the environment of the embryo. The same holds true of the specimen which I have described. In later embryos (Leopold, Merttens, etc.) the decidual increase in the cells is still imperfectly developed, and even at the sixth week it is found well marked only in the compact layer of the decidua vera (Webster). The maximum development in the vera is attained at the end of the second month (Klein), between the second and third months (Webster), or between the third and fourth months (Whitridge Williams). The change progresses up to a certain point with the duration of pregnancy. The conditions present in Peters' specimen justify the conclusion that the decidual increase is dependent on a stimulation of the stroma cells by some influence emanating from the fœtal cells. This stimulus, at first located to the region of the engrafted ovum, soon extends the sphere of its influence. The more distant regions of the uterine mucosa come gradually under its sway, until, at the stage which corresponds to the completion of the decidual change, the fœtal influence has reached the maximum of its power.

What are the nature and the source of this fœtal influence, and how is it disseminated? The exact nature of this influence is still a matter of conjecture, though there would seem to be little doubt that it consists of some substance of a chemical nature, probably a ferment or ferments, the results of which are the complex of maternal tissue changes which characterise pregnancy. The origin of the influence which determines the decidual change we know with certainty. The fact that it is well marked in the maternal tissues where only the

chorionic cellular layers are present, *e.g.* chorionepithelioma, proves that it originates in the ectodermic cells, and not in the fœtus or the mesoblast of the chorion. As regards the mode of its dissemination to regions distant from the actual site of the ovum, it is clear that this may be accomplished in one or other or both of two ways. It may be due to a passage by direct extension through the tissues, by a process of diffusion, or it may be carried by the blood-stream. In support of the first mode of transmission is the fact that in Peters' early ovum the change which is present in the mucosa only in the proximity of the chorion has, however, involved the tissues at some little distance from the embryo. The fact that in tubal pregnancy the wall of the tube is invariably the seat of the degenerative and decidual changes at a considerable distance from the ovum bed, and that in the process both the arteries and veins are affected, would suggest that there must be a certain amount of direct diffusion through the tissues. The same is seen in chorionepithelioma. On the other hand the extensive involvement of the uterine mucosa in the decidual change would suggest that there must be a certain degree of blood dissemination. This fact is also suggested by the occurrence of a decidual transformation of the mucosa of the uterus or of the opposite tube in tubal pregnancy, and of the occasional development of a decidual change in the tube in uterine pregnancy. It would seem that to satisfactorily account for these phenomena we must admit the occurrence of a spread of the chorionic influence by the blood-stream.

The occurrence of a decidual change in pregnancy in the mucosa of the uterine body, and, except in rare instances, its absence in the cervix and distant regions, and its occurrence in a marked degree only in the uterine mucosa and the tubal mucosa in many cases of tubal pregnancy, demonstrate beyond doubt that for its development there must be a susceptibility on the part of the tissues. The structural necessity for the presence of a well-marked decidual reaction is that the tissue must approximate in character to that of the uterine mucosa. This essential is presented only by one other tissue, the mucosa of the tube. In each case the stroma is of a peculiar, undifferentiated embryonic type. We have seen that it is the soft, displaceable nature of this tissue which permits, in the uterus, of the ready opening up of the vessels and an œdematous hæmorrhagic escape into the stroma during menstruation and pregnancy. Does it not seem strange, to say the least of it, that the only region where, in normal pregnancy, the blood and dropsical escape has occurred to any extent is the vicinity of the

embryonic structures, whereas, as is seen in menstruation, the uterine mucosa is obviously constructed to allow of a ready blood escape at any part of its surface? Does not the coincidence, namely the existence of a blood escape which is definitely localised in one place, the other regions of the stroma remaining blood free, assume proportions which are remarkable when we note that the extraordinary increase in the stroma cells which occurs during the decidual change would seem to be able to effectually prevent such a blood escape except in the region of the implantation cavity, if there were any tendency to its occurrence? This question I shall again raise in the next section of this investigation.

In a previous chapter I have referred to the fact that a comparison of the maternal changes present in the different early ova suggests that the mucous membrane of the uterus in different women, or more probably in the same woman at different times, varies in its susceptibility to the decidual change. The degree in which this is exhibited is in the earliest stages not necessarily proportional to the duration of the pregnancy. The same is true of the decidual change in the mucosa of the pregnant tube.

Structure of the Uterine Decidua

In an enlargement of the stroma cells in the decidua vera many differences in the resulting changes are found. In some cases the cells are round, oval, or polygonal in shape, in other instances they are spindle shaped, often being drawn out to a remarkable degree. In some cases they are separated from one another by distinct spaces, and they are then often seen to be united by protoplasmic outrunners of the cell bodies. The intervening spaces may be clear or they may be occupied by a granular or fibrillary material which stains with eosin. It is probably coagulated serum. In many places leucocytes and cells which look like unaltered stroma elements are seen lying between the decidual cells. Between these smaller cells and the largest decidual elements it is easy to detect all gradations in size. To some observers (Marchand, Rossi-Doria) these appearances indicate an active transformation of the one size of cell into the other. They have described mitotic figures which would indicate that there is associated with the change an active proliferation. Whilst my specimens confirm their interpretation of the *rôle* of the smaller cells, I have been unable to detect the presence of the mitosis. On the other hand in many places

cells with double nuclei are visible, which in several instances would seem to have been formed by a process of direct nuclear division. The fact that there is evidence of a proliferative change associated with the decidual increase in size of the cells would tend to bring these observations in line with those recorded in connection with the pregnant tube. We there saw in some locations a distinct hyperplastic change conjoined with the decidual enlargement of the cells. In the respect just mentioned my specimens accord with the changes described by many other observers.

In many regions of the decidual membrane the cells are packed close together, and the shapes they assume are obviously due to mechanical pressure against one another. The degree of expansion of the cells, which varies within wide limits, would seem likewise to be determined in some places by factors purely mechanical in nature. For example, it is often possible to detect a smaller cell wedged tightly between surrounding larger cells, whose pressure would seem to have prevented its further expansion.

In many places the cells have attained an enormous size, and then they are usually seen to be packed tightly together. Between the distended glands in the spongiosa, on the other hand, the same dense packing together is often seen where the cells are comparatively small.

In the chapter devoted to the structure of the endometrium I advanced the belief that the entire extent of the stroma, including the intimal and outer cells of the vascular walls, is composed of an undifferentiated embryonic material, connective tissue in nature. In support of that view I was able to demonstrate, I believe without doubt, the structural similarity between the endothelium and the stroma. It was shown, also, that during menstruation the intimal cells are easily separated from one another, and, with the surrounding stroma, are often displaced to form the walls of a newly-formed blood space. This process is often associated with a suffusion of the surrounding tissues with fluid and red cells. The same observations were shown to apply to the outer supporting cells of the vessel wall. In the mucosa, except at the part immediately abutting on the muscle, there is an absence of elastic or muscular tissue in the vessel walls.

The study of the pregnant tube and of the chorionepitheliomatous uterus was found to give additional support to this conception by indicating the existence of a structural and functional identity between endothelial and connective-tissue cells in general. In these regions we found this similarity again appearing in the perfect resemblance

between the two elements in their response to the chorionic influence. In each there was apt to be a fluid imbibition or a decidual enlargement, and in some cases the connective-tissue cells were seen to function as endothelium.

Do those observations coincide with the appearances revealed in the decidual membrane? It is clear that, in the marked deviation of the mucosa from the ordinary condition which characterises the pregnant state, we should have an opportunity of putting the above interpretation to the test.

In many places the blood-vessels are lined with cells which correspond in every respect to those in the surrounding decidual tissue. This is chiefly the case in the distended vessels. In these the decidua may come right up to the blood. In other vessels, and this is the usual condition, the lining layer is formed by flattened and elongated cells, similar to the endothelium in the resting state. It is obvious that the former appearance is due either to the fact that the endothelial cells of the blood space have been detached and have disappeared or to the fact that they have become enlarged in a decidua-like manner. If the latter interpretation be true, the existence of an unaltered endothelium in the case of other vessels must, in all probability, be due to some difference in circumstance which has determined the retention by the cells of their wonted size and shape.

If the endothelial cells in the uterine mucosa are immune to the decidual changes, they must differ in their structure and their mode of response to the chorionic influence from the endothelial cells in the tube. Here we saw in many places a definite enlargement of the cellular elements in a decidual manner, and this both in the vascular endothelium and that in relation to the peritoneal surface. That there does exist such a structural difference between the endothelium in the two sites is, on the face of it, unlikely. The exact similarity between the two structures in their reaction to the fœtal influence is, moreover, not difficult to demonstrate. In proof of this I submit the following observations:—

(1) In many places, as I have said, the vessel lumina are found to be lined by a layer of cells similar in every respect to the surrounding decidual elements (Fig. 63). It is unlikely that this appearance is due to a detachment and disappearance of the unaltered endothelium, because, whereas in the same sections many of the vessels are lined by cells apparently unchanged, there is no trace of the process in action. Under these circumstances one would expect to find in some locations a

cellular separation occurring if by this means we are to explain the appearances.

(2) In many places one can actually see the decidual enlargement of the cells in the process of occurrence. On Fig. 64 is seen a vessel from the decidua vera on the side of the uterus opposite to that occupied by the placenta. Here we see a marked proliferation of the endothelial lining, which has resulted in the projection into the vessel lumen of masses of the cells. Their appearance negatives the possibility, which otherwise might have been entertained, that they are chorionic cells. The nuclei are smaller, and in staining reactions they correspond to the surrounding decidual cells. Their site, also, throws this interpretation completely out of court. The cellular mass can be traced through a number of sections, and the change can be detected throughout a long extent of this vessel. It can also be seen in several other of the vessels. So far as I know it has not previously been described in the decidua vera.

The appearance obviously indicates the presence of an active endothelial proliferation. The point to which, however, I wish to direct special attention is the large size attained by the cells, many of which are as large as some of the increased cells in the adjacent decidua. The change is, without doubt, of the same nature as that exhibited by the elements of the stroma. The division of the cells is, in all likelihood, by an amitotic nuclear fission. In no place could I detect mitotic figures. In many of the cells the nuclear division can be seen in the process. In this respect, again, they thus coincide with the surrounding stroma elements, where the same nuclear changes are present.

(3) In some sections, also, I have been able to detect similar changes *in the vessels in the muscular coat.* In Fig. 66 is represented such a vessel. This was present in a different specimen. Here there is seen on either side a cellular mass projecting into the vessel lumen. The masses are attached to the vessel wall and are obviously endothelial in origin. In appearance and staining they differ widely from the fœtal cells. In this specimen they have undergone a greater degree of enlargement than in the last specimen. They are undoubtedly to be looked upon as decidual cells. In another part of the same vessel the endothelial vacuolation, to which I have repeatedly referred, is to be seen. The wall of the vessel and the surrounding tissues in this case are involved in an œdematous escape.

These observations seem to me to demonstrate beyond doubt that the uterine endothelium has the faculty of exhibiting a decidual change in a manner as perfect as that of the stroma cells. As in the stroma, it is

clear that here, also, the decidual alteration is intimately bound up with a definite proliferative process. In these respects the uterine endothelium corresponds to the tubal endothelium.

THE FUNCTIONS OF THE DECIDUAL MEMBRANE

The theories advanced in the literature to explain the functions of the uterine decidua may be grouped under one or other of two headings: (1) it is laid down as a barrier against excessive fœtal invasion of the maternal tissues; (2) it serves as a storehouse for nutriment, which is absorbed by the growing fœtal cells. The orthodox conception of the functions of the decidua is thus expressed by Whitridge Williams in his text-book of *Obstetrics* (1908): "The function of the decidua may not merely be to afford a suitable structure for the implantation and nutrition of the ovum, but also to protect the maternal organism against invasion by fœtal tissues." The idea that the decidual cells have a nutritional function to perform is to some extent supported by the results of histological and experimental researches in the lower animals. It would seem not unlikely that the decidua has in some animals (rabbit) a definite function to perform in connection with the glycogenic metabolism (Bernard, Godet, Maximow, Chipman, Lochhead, etc.). The cells in the maternal part of the placenta are seen to act as a secretory mechanism and a storehouse for glycogen, which is apparently directly taken up by the advancing fœtal elements. The same may be true for fat (Eden, Chipman, etc.) and other food substances.

The other explanation of the decidual function, namely that it prevents an excessive fœtal invasion, is, in a sense, directly antithetic to that just mentioned. In the one case the cells act as a deterrent to the chorionic growth, in the other case, by providing nutrition, they would actually foster this growth. Neither of these explanations accounts for the presence of the decidua vera. The decidua serotina, I believe, contributes largely to the limitation of the growth of the fœtal ectoderm into the maternal tissues, but in a different manner than is usually believed. The decidua reflexa clearly serves the function of shutting in the ovum cavity and the intervillous blood space. In view of the early atrophy of the fœtal villi in relation to this part of the decidua, it is impossible to conceive that the complete transformation of the uterine mucosa to form the vera is for the purpose of preventing a wholesale invasion of the uterine wall. The fact that, so far, this part of the altered mucosa has not been associated with a definite function is

candidly admitted in the following words :—"We are unacquainted with the functions of the decidua vera" (Eden, *Manual of Midwifery*, 1908).

It seems to me that the nature of these functions is to be found in the investigations which I have recorded in connection with the mode of the chorionic action on the maternal tissues. The precise nature of this activity we have seen in the abnormal regions studied, and the conception that in the uterine mucosa the same processes are in operation has been reinforced by the study of the early decidua in several young ova.

I have shown that in the pregnant tube and in the uterine wall, the seat either of a simple or a malignant chorionic involvement, definite tissue and vascular changes were present. These consisted in a widespread œdematous and blood escape from the vessels, associated in many cases with a wholesale teasing asunder of the vessel walls and a gradually increasing expansion of their cavity. These conditions, whilst most marked in the immediate vicinity of the fœtal ectoderm, were present even at a considerable distance from this. The chorionic influence, in all probability, to be identified with an enzyme or enzymes, has led to a softening and solution of the muscle, etc., and, what is more important in so far as the analogy with the uterus is concerned, to an active imbibition of fluid by the endothelial and connective-tissue elements. In all these locations I have pointed out that a decidual change in the surrounding connective-tissue elements tends to prevent these irregular and uncontrolled vessel and tissue changes. The influence of this decidual change was demonstrated in a manner which leaves little room for doubt in the pregnant tube. *Here it was found that the only regions of the tubal wall which had resisted the changes were those with a decidual enlargement of the connective-tissue cells.* This in some cases was present in the vessel wall (Fig. 37). In other cases it was present in the tubal folds. On Figs. 31, 32, 33 are shown a representation of the conditions present. Whilst the muscular coats and the thick walls of a large vein are opened out by œdema and blood dragged out as the result of the tissue changes, and *this even at a considerable distance from the embryo*, the stiffening of the connective tissue of the mucosa by the marked decidual enlargement of the cells has completely prevented the process. *The appearances, at first sight, suggest that this is due to the support given to the vessel walls and the surrounding tissue by the dense packing of the altered cells.* This point I shall discuss at greater length subsequently.

Is there any evidence that such a function is subserved by the

uterine decidua? Here we have seen there are changes which indicate the existence of protoplasmic changes of the same nature as those which have, in the other sites, led to an uncontrolled blood escape and an irregular and increasing vascular expansion. That here, also, the decidual change in the cells is intended for a limitation of these changes is convincingly demonstrated by a comparison of the maternal tissues in the neighbourhood of the ovum in Peters' case, and in that which I have described, with those with a more marked decidual reaction. Whilst in the former, where the decidual process is in its initial stage, there is a wholesale and irregular ploughing up of the immediate tissues by fluid and blood, and an enormous and increasing vascular distension, in the latter the changes, though present to some extent, are much more limited. In a still later stage they become completely or almost completely lost (compare Plate XIX. with Fig. 67).

The ultimate cellular changes associated with the decidual condition are still beyond our grasp; any explanation must be in the main conjectural. It would seem, however, clear that the increase in the cell contents associated with the change must be derived from the blood. In fact we are inevitably forced to the conclusion that in the change we have a positive indication of a tissue alteration which has resulted in an active and an extensive assimilation of material from the blood-stream. This may be directly furnished by the blood-vessels or it may partly be lymphatic in origin. In this consideration it seems to me that so far we have a strong analogy with the process which I have advanced to explain the manner in which the maternal vessels are opened up during pregnancy. This, I have indicated, is probably dependent on protoplasmic tissue changes which determine an active imbibition of the blood (fluid and corpuscles) by the uterine stroma. The analogy between the two processes ceases at the immediately succeeding stage, for whereas in the one case the fluid absorbed remains unaltered in consistence and as such can pass freely through the tissues, in the other it is built up by the cell into its substance. The necessity of this is obvious—it prevents the œdematous teasing out of the vessel wall and the occurrence of an irregular blood infiltration at regions where its presence would be not only unnecessary but injurious.

The exact manner in which the change advances in the decidua vera is still imperfectly worked out. Different observations in early cases would tend to indicate that it commences in the surface part of the mucosa and advances in an outward direction towards the spongiosa. This would seem to be due to the fact that in the superficial parts a

spreading out of the stroma is more easily accomplished (*cf.* menstruation and many pathological conditions). Here, also, the vessel walls are thinner and correspondingly easier of separation with a permission of the fluid escape.

What is the significance of the proliferative change present? As has been suggested by other observers, it may indicate the means by which the stroma is recuperated for the death of the decidual elements, many of which, especially after the first few months, are seen to be degenerating. It must also be considered as an accessory means by which the implantation cavity undergoes the increase in length necessary to keep pace with the increase in the size of the ovum.

Decidua Serotina and Reflexa—Cause of Limitation of Chorionic Invasion

If the conclusions just formulated be justified, we are enabled to appreciate the manner in which the fœtal elements are prevented from irregularly infiltrating the maternal tissues. We shall, perhaps, better understand this by recalling the analogies presented by the pregnant tube and the fœtal invasion of the maternal structures seen in chorion-epithelioma. When a mass of the fœtal elements in either of these regions comes into contact with the mother's tissue there occurs a softening and in many cases, especially where muscle is included, an actual solution. The important result of this action from our point of view is that there is an active "imbibition" of fluid by the affected part. This may be derived either from the space in which the chorionic cells lie (*e.g.* a vessel) or it may be passed across the tissue intervening between these and a neighbouring vessel. In either case the essential element for the nourishment and growth of the fœtal cells (*i.e.* the blood fluid) is obtained. It is the presence of maternal fluid or blood at a given point which determines the chorionic increase.

In the decidua the change in the cells has prevented this softening and fluid infiltration of the tissues. For this reason the food necessary for the growth of the fœtal elements into their midst is wanting. When they come into contact with the resistant tissues their development is arrested. We thus see that the decidual change, which is provoked by the fœtal influence, has in this region functioned in exactly the same manner as in the other decidual regions, *i.e.* it has prevented the tendency to an active transference of fluid into and through the tissues. We thus see that the function of the serotina

and reflexa is to act as a barrier to the fœtal invasion, but only in so far as we have indicated.

The rationale of this action is clearly indicated by comparing the effects of the chorionic activity in the pregnant tube and in chorion-epithelioma with those present in the decidual membrane. I have referred to the softening and fluid separation of the tissues which occurs in advance of the chorionic cells in the former cases. In the vessels this fluid imbibition is often associated with an aneurismal expansion of their lumen—the wall in the process receding from the fœtal cells where these are in the cavity. Teacher, who, I believe, first described this condition, rightly saw in it an analogy to what occurs in the production of the normal implantation cavity of the ovum. His interpretation of the details of this analogy I have advanced reasons to show was imperfect. I have pointed out that the change is by no means confined to vessels containing the fœtal elements. It is wide-spread, and it is often seen to result in a wholesale advancing of the vessel spaces toward the chorionic cells (*cf.* Peters' ovum). It seems to me that this latter process more accurately accords with the manner of production of the implantation cavity—that it is an opening out of the tissues in advance of, rather than a destruction by, the embryonic cells.

If such be the case, we have a further explanation of the decidual function. As shown by the Bryce-Teacher specimen, it early reaches a degree in the vicinity of the ovum well-nigh perfect. It must then prevent a further increase in the implantation chamber in the way we have mentioned, and which is associated with a displacement and thinning of the underlying stroma. *The enlargement of the cavity then must be due, not to a destruction, but to a hypertrophy, of the walls* (*decidua and muscle*). This, it seems to me, is absolutely certain. If it were otherwise the uterine wall would soon be thinned out and destroyed. We can now appreciate the importance of the proliferative change. By an increase in the decidual and the muscular elements there occurs the gradual expansion of the uterine wall and the enclosed gestation cavity.

The effects of the decidual change in preventing the above-mentioned tissue softening and displacement is well shown by comparing Fig. 68, which shows a chorionic mass within and in contact with the walls of a decidual vessel, with the results seen in the case of a similar mass in a similar situation in the pregnant tube or in chorionepithelioma (Fig. 54). If I am justified in the employment of the analogy, and I am, in this

respect, following in the footsteps of most previous observers, it seems to me that the demonstration is conclusive.

Whilst limiting the extent of the above-mentioned tissue changes, whilst preventing an excessive displacement and thinning out of the mucosa underlying the ovum, and, at the same time, an irregular fluid and blood infiltration of the stroma, the decidual change in no way interferes with the presence of the intervillous space, in which the fœtal elements are richly supplied with the maternal blood, and in which they undergo the marked proliferative changes which we associate with the human placenta. It is, at first sight, difficult to understand how it is that the enormous increase in the stroma in consequence of the decidual change, due to the cellular enlargement and the cellular proliferation, does not encroach on and even obliterate the intervillous space. We have seen the change well marked even in the very early stages of the imbedding process, when the implantation chamber scarcely measures 2 mm. in its longest diameter (Bryce-Teacher ovum). The extraordinary increase in volume of the mucosa associated with the decidual alteration is emphasised when we remember that not only does it increase *pari passu* with the increase in the length of the uterus, but it actually, in the early months, increases out of proportion to this. The difficulty, it seems to me, is the same as that associated with the fact that, in spite of the increase in volume of the surrounding stroma, the vessel lumina are not encroached upon, at any rate, in the large majority of cases. What is the secret of this?

To account for these phenomena I would advance the following explanation:—From what I have pointed out in a previous section of this investigation it seems likely that in a given area of the stroma the decidual increase in the cells only occurs to an extent strictly proportional to the degree in which there has occurred, or in which there tends to occur, an opening out of the structures. This fact amply accounts for the absence of the change in the supporting cells of the more condensed vessel walls, and it accords with its occurrence in the vessels which seem to have opened out. If this be true we can understand how it is that the integrity of the lumen is preserved. The same will apply to the intervillous space.

The investigations which I have recorded enable us to recognise in the decidual membrane a function which may be regarded somewhat arbitrarily under three headings, according to the three different maternal changes provoked by the extrachorionic activity. There can be no doubt that the alteration which the stroma cells undergo in the

decidual enlargement is associated with a change which annuls the special susceptibility, which the protoplasm of the mucosa possesses, to react to the chorionic influence by actively dragging out the blood fluid and cells from the vessels. Once the cell has assumed the definite decidual character this faculty disappears. With this disappearance there is established a limitation of the maternal changes which are essential to the imbedding process.

(1) In the first place, with the development of the definite decidual change the mucosa vessels become more and more supported. The opening out of their walls, in the way which I have described, is now prevented from occurring to an excessive degree. The decidual alteration limits at once the sinus-like expansion of the vessels and the pouring of the vessel contents into the implantation chamber.

(2) The change in the stroma cells prevents an excessive tearing up of the maternal tissue with fluid and blood. The decidual increase in the stroma is associated with a diminution or obliteration of the fluid spaces, which have been formed at an earlier stage of the process. That this occurs is proved by a comparison of the maternal tissue in the neighbourhood of the ovum in the earliest stages (Plates XIX., XX.), when, as we have seen, there is an irregular and marked spreading apart by œdema and blood, with the same tissue at a stage when a definite decidual membrane has been formed (Fig. 67). The exact manner in which the red blood cells are got rid of it is difficult to say. They may pass back into the vessels or they may be removed by the enlarging stroma cells.

(3) By abolishing the special susceptibility of the stroma protoplasm to "imbibe" the blood fluid in response to the extrachorionic influence, the decidual change also limits the expansion of the implantation chamber by the process which is responsible for its formation. It is clear that were it not for some protective arrangement the tissue displacement, which probably determines the production of the early chamber, would soon thin out the mucosa to a dangerous degree. After the decidual change is definitely established the increasing expansion of the cavity must, as has been pointed out, occur by an entirely different process.

The uterine decidua, consisting as it does of large cells densely packed together to form a compact tissue, is clearly, from its structure, so adapted as to resist the ready opening out by fluid and blood which can occur in the loose, displaceable tissue composing the unaltered stroma.

Whilst the function of the decidual membrane such as I have

formulated would seem to be definitely established, the investigations, which I have recorded, open up side issues for interesting and profitable research. Amongst others I would mention two. The first I have already touched on. What is the ultimate nature of the protoplasmic changes that dominate the maternal reaction to the extrachorionic influence, and what is the relation between the increased affinity for the blood fluid, which we have seen to be the most important change, and the decidual increase in the cells? We have seen that in the regions of abnormal chorionic activity (pregnant tube, chorionepithelioma, etc.) the maternal tissue changes, whilst all traceable to the same common alteration in the protoplasm, vary in their nature between a process which is associated with an active formation of new vessels and a wholesale degeneration and solution of tissue. In the uterine mucosa the same difference is seen, but here the gross degenerative changes are less marked, and, on the whole, the reaction is no more degenerative in nature than is that which is responsible for a new-vessel formation.

The second problem which suggests itself is one which will require solution before anything like a complete description of the maternal changes can be given. The researches, which I have recorded, indicate that the maternal changes are determined by a chorionic material or materials, which pass further and further into the mucosa by a process of diffusion and probably also *via* the blood-stream. The finely adjusted constitution of the entire stroma, which determines the susceptibility of the mucosa to the cytoplasmic change associated with an enhanced attraction for fluid, which I have shown to be exhibited with certainty in connection with the menstrual function, and which I have also described in the mucosa round the young ovum, implies that with the increase in the duration of pregnancy gradually more and more remote areas of the mucosa will react to the extrachorionic influence. Were it not for some provision such as the decidual change introduces, it is easy to see that nothing could save the mucosa from an extensive and uncontrolled tearing up of the stroma throughout its entire extent by the expanding vessels and the œdema and hæmorrhage. This consideration amply explains the necessity for a decidual transformation of the stroma throughout the entire endometrium, from fundus to internal os, *i.e.* throughout the entire tissue, which is especially adapted to react to the chorionic materials. It is by virtue of this change that the serotina, reflexa, and vera are all enabled to perform their functions.

Whilst on these points there can be no doubt, the exact nature of

the changes induced in the mucosa, as more and more distant areas are subjected to the extrachorionic influence, is still uncertain. This constitutes the second problem which will demand investigation. In the vicinity of the ovum we have seen that the maternal changes consist in an increase in the quantity of blood present, in the shape of expanded vessels and a fluid and hæmorrhagic infiltration of the tissues. This is followed by a decidual limitation or obliteration of these changes. Does this sequence of events hold true with regard to the more remote areas of the mucosa? That it does to a certain extent is indicated by the fact that throughout the entire decidua there are formed the expanded vessels, and that in many places, even under normal conditions, there is often seen an œdematous and a hæmorrhagic infiltration of the stroma. This is especially the case in the younger specimens, and is the less marked the older the decidua. In spite of this, however, it seems to me not improbable that the sequence which occurs in the vicinity of the ovum, and which is essential to the imbedding process and the early nutrition of the ovum, may be modified in regions where it is not required, and that here the decidual change may dominate the process and prevent at any stage the extensive spreading apart of the tissues by the blood fluid and cells, which occurs in the proximity of the implantation cavity.

Summary of Maternal Changes in Pregnancy and the Functions of the Decidua

(1) In the uterine mucous membrane and muscular coat during pregnancy there is evidence of a widespread tissue change, tending to lead to an opening-up of the vessels and an irregular œdematous and hæmorrhagic escape. It is present throughout the entire extent of the uterine wall, and it is due to the gradual extension of the chemical substances elaborated by the fœtal cells, which constitute the extrachorionic influence. This extension occurs by a direct passage through the tissues or by a circulation along the blood-stream.

The stroma of the uterine mucosa is especially constructed to permit a ready occurrence of a blood escape at any part of its substance. This takes place periodically as a widespread œdema and hæmorrhage during the premenstrual and menstrual phases in response to some substance reaching

it *via* the blood-stream, which alters the protoplasm in such a way as to lead to an active "imbibition" of the blood fluid and corpuscles. We have seen that the same changes occur in the mucosa round, and at a considerable distance from, the early ovum, and they are induced at a considerable distance from the fœtal elements as the result of the extrachorionic influence in chorionepithelioma and in placental fragments, where the amount of the liberated chorionic substances must be smaller than that spreading from the fœtal structures during pregnancy.

This special susceptibility of the uterine mucosa to these tissue changes must be controlled in some way during pregnancy, otherwise there would inevitably be an œdematous and hæmorrhagic escape throughout its entire extent.

(2) In the abnormal regions of chorionic activity the only sites where the limitation of these vascular and tissue changes has occurred are the places where there has taken place a decidual enlargement of the connective-tissue cells. This is especially evident in the mucous membrane of the tube. The decidual change in the tube is usually poorly marked, and there is invariably present an opening-up of the vessels, a tearing-up by œdema and hæmorrhage, and a solution of the tissues even at a long distance from the fœtal cells. There is likewise an irregular and increasing expansion of the vessels in the tubal wall in response to the same tissue changes.

(3) In the mucosa during pregnancy the tissue changes to which I have referred are limited to the region of the ovum subsequent to the development of the decidual membrane.

As the result of these investigations we are able to state with the greatest possible certainty that the function of the decidual membrane is to prevent an irregular and increasing opening-up and expansion of the maternal vessels and a tearing-up of the mucosa by fluid and blood after the tissue changes necessary for an adequate supply of the maternal blood for the engrafted ovum have been accomplished. It is by virtue of this action that the chorionic invasion of the tissues is limited, and that the increase in the implantation chamber is prevented by an erosion or displacement of tissue. These considerations thus amply account for the necessity of a complete decidual transformation of the entire stroma (*i.e.*

the entire susceptible tissue), and they provide an explanation of the functions of the serotina, reflexa, and vera.

The changes in the muscular wall are exhibited in the softening and increasing expansion of the fine vessels which occur. They are limited by the muscular tissue, which undergoes an increasing hypertrophy.

APPENDIX

ŒDEMA

THE changes which occur in menstruation, in uterine and tubal pregnancy, and in chorionepithelioma, with which we have been concerned in this work, are intimately bound up with the study of the cause of the escape of fluid from vessel to tissue. In this place I propose, for the sake of reference, to outline the position which this problem occupies at the present day, with a *résumé* of the data which the foregoing investigations have supplied.

The explanations advanced to explain a passage of fluid across a vessel wall fall into one or other of two classes, namely the Vital and the Physical or Physico-chemical.

1. *Vital Theory*

According to this theory, which is especially associated with the name of Heidenhain, the fluid is secreted by the endothelial cells. A theory which does not attempt more than an explanation of such a nature can obviously never be of much use in an endeavour to explain the ultimate tissue changes. That it fails to embrace all the factors responsible for the production of œdema is conclusively proved by the fact that the connective-tissue elements play as important a *rôle* as the endothelium. This I have shown in connection with menstruation and pregnancy.

2. *Physical and Physico-chemical*

(*a*) According to the *pressure* or *filtration* hypothesis, first advanced by Ludwig, variations in the amount of fluid present in the tissues are supposed to depend on variations in the pressure of the circulating fluid, an increase in the pressure leading to a forcing out of the water. Whilst it is impossible to deny that this mechanical factor may play a certain part in the process, it has long been recognised that to explain all the phenomena other processes have to be invoked. The first of these to be noticed is the

(*b*) *Osmotic Theory.*—This may fairly be said to be the explanation most widely accepted at the present day. This contribution towards the study of the subject we owe in the main to the plant physiologists, especially Pfeffer, de Vries, Hedin, Hamburger, and Höber. It has been applied to animal physiology by many eminent workers, *e.g.* Koranyi, Starling, etc. This explanation explains the passage of fluid from the vessels by the fact that the functional or pathological changes in the tissues, as the case may be, lead to the formation or liberation of elements in the cells or tissue spaces that enhance the osmotic tension. This results in a continual streaming of fluid from vessel to tissue so long as there is an osmotic pressure discrepancy, and so long as there are present complete films corresponding to the colloidal membranes of *in vitro* experiments.

An essential for the application of osmosis, as ordinarily understood, to the animal cell, is the existence of such a colloidal membrane which will retain the materials in solution (called vaguely "crystalloids") but which will be permeable to the dissolving fluid. The fact that such a cell membrane is absent in most animal cells and the finding, moreover, that when the cell contents are squeezed out into a solution these behave exactly as the original cell, suggest strongly that osmosis, as ordinarily understood, is inapplicable to the animal cell. Another experimental fact of importance in this connection is the discovery that the cells behave differently in the amount of fluid taken up or given off when brought in contact with solutions of different substances having the same osmotic pressure. This at once places the water interchange between cell and solution in a category different from osmosis as studied *in vitro*. It is difficult, in addition, to explain by osmosis the free passage of dissolved substances both from and into the cell, processes which must be continually in action to carry off the waste products and to supply the cell with its food materials. These considerations have led to varying ideas regarding the hypothetical cell membrane. Overton, for example, has shown that a number of substances in solution, *e.g.* urea, glycerine, do not lead to a shrinkage of the protoplasm of plant cells. Salts in solutions of suitable strengths, by attracting the intracellular water, lead to a shrivelling of the cells. Overton believes that the behaviour of the cells towards the former materials is dependent on the fact that these can pass across the membrane surrounding the cells. He has shown that the substances which act in this way are soluble in fats or fat-like bodies, and he has therefore assumed that cells are equipped with a membrane consisting

of such fatty materials. This hypothesis is supported by the existence of the lipoids in cell protoplasm, *e.g.* lecithin, cholesterin, etc. This explanation, it is clear, fails to account for the transmission of many other substances which must enter and leave the cells. Nathansohn has, for this reason, suggested that the surface of cells consists of different areas, which retain, some one material, some another.

Within more recent years attempts have been made to overcome the difficulties of reconciling with osmosis the water interchange between cell and surrounding fluid. According to this class of investigations a defined surface membrane is unnecessary. The chemical constitution of the cell protoplasm as a whole it is that determines the changes which enable it to attract or to give off fluid. "The whole chemical structure of the cell and that part of it which is physiologically active is the osmotic machine, and needs no membrane permeable or impermeable in order to exhibit the usual osmotic phenomena of shrinking or swelling, leading finally to disruption. . . . In all cases the nature of the bioplasm is so differentiated chemically as to form a dividing surface readily permeable to the solvent, and this is all that is required, in addition to the varying unions or holding powers between the cell colloids and crystalloids, to establish an osmotic cell. As an example of what is meant here we may instance the swelling of fibrin, connective tissue, and gelatine under the imbibition of water. Between gelatine and water there is no structural membrane with semipermeable pores, yet the gelatine takes in water in a truly osmotic fashion, and the pressure developed, if the swelling and uptake of water are resisted, is very high" (Moore *).

In an investigation on the problem of œdema Fischer † says: "We will encounter no difficulty in explaining the various experimental facts at our disposal by ignoring altogether the existence of impermeable or partly permeable cell membranes and simply remembering that the substance of a cell consists of a mixture of different colloids."

The investigations which I have recorded on the preceding pages of this book (and which, so far as I know, constitute the first attempt to explain the mode of production of œdema by a histological survey of the tissue changes), have demonstrated beyond doubt that the fluid escapes from the vessels, not in response to a mechanical filtration, but in

* Moore, "Equilibrium of Colloid and Crystalloid in Living Cells," *Further Advances in Physiology*, Arnold, 1909.

† Fischer, "Œdema," *Trans. Coll. Phys.*, Philadelphia, 1909. (See this work for the literature.)

consequence of an alteration in the tissue protoplasm which determines an imbibition of the blood fluid. It is difficult to imagine a tissue more favourable for the study of the mode of production of œdema than the uterine mucosa. As I have pointed out, the main component of this (the stroma) is composed throughout of an undifferentiated mass of soft, easily displaced protoplasm, which is especially adapted to react to certain chemical substances by actively imbibing the blood fluid. This is dependent on a change in the colloids that enhances their affinity for fluid. This passes into the protoplasm and expands the intercellular spaces. In addition, the perinuclear masses of protoplasm are broken up into minute fluid-containing cavities surrounded by the displaced cell substance. These increase in size, partly by expansion, which is followed by a giving way of the tissue partitions and an amalgamation of adjacent spaces, and partly probably by an actual solution of tissue. These changes are well marked in menstruation and pregnancy, and determine, amongst other changes, the formation of the large œdematous and blood areas and the expanded sinuses, which develop in these conditions. I have described similar changes in the pregnant tube, in the chorionepitheliomatous uterus, etc.

It is clear that, in the case of an œdematous accumulation in the protoplasm, where the hydrostatic tension of the fluid may be comparatively great, a complete membrane is necessary to retain the fluid after it has passed into the cytoplasm in an endeavour to satisfy the increased water-affinity of the colloids. This consideration in no way conflicts with the statements of Moore, Fischer, etc., that it is the chemical constitution of the protoplasm as a whole and the changes which it undergoes, and not the presence of a colloidal membrane limited to the surface, which determines the entrance of the water. In fact my investigations coincide accurately with the conclusions to which their experiments have led them. The stroma of the uterine mucosa is so constructed as to permit of a fluid accumulation at *every* part. In many instances it is possible to determine with certainty that the small mass of protoplasm surrounding a nucleus may be broken up into a large number of fluid-containing spaces.

It would seem equally true that in the process a certain amount of the altered protoplasmic material passes into solution in the fluid. It is the "crystalloidal" content of the solution, which is separated from the surrounding medium by the membrane formed by the displaced protoplasm, that, as it were, fixes the fluid and tends to lead to an increasing accumulation till the altered colloids are satisfied. This

explanation of the phenomena must, however incomplete it may be, be so far true, and it explains how in the microscopic changes which are produced the appearances at first sight suggest the existence of an osmotic process.

If this conception of the manner in which an œdematous accumulation in the tissues occurs be accepted, it lends added support to the nature of the intercellular spaces of the endometrium such as I have described them (Chapter I.). I have shown that the histological appearances indicate strongly that these do not consist, as is taught, of spaces which communicate freely with one another, but that they correspond to fluid-containing spaces which are completely walled in on every side. The so-called protoplasmic threads passing between adjacent cells are in reality uninterrupted films, the stroma corresponding in its structure to the arrangement present in a soap-froth, which consists of an immense collection of complete air-containing cavities. Only by an interpretation of this sort, if the recent conceptions regarding œdema be correct, is it possible to explain the marked expansion of the intercellular spaces which occurs during menstruation and pregnancy, where the fluid is clearly present under a considerable hydrostatic tension.

As indicated on former pages, I believe that the protoplasmic changes responsible for the œdematous dragging of the fluid from the vessels in the regions referred to accounts for the formation of the new capillary vessels. This is dependent on a drawing of the fluid and blood along intracellular canals formed by an amalgamation of the fluid spaces produced in the way that I have mentioned. These changes are often associated with a proliferation of the tissue elements.

BIBLIOGRAPHY

Structure of Uterine Mucosa and Menstruation

Aveling. *Obstetr. Journ. of Great Britain and Ireland*, July 1874.

Bischoff. "Beiträge zur Lehre von der Menstruation und Befruchtung," *Zeitschr. f. ration. Medizin von Henle und Pfeufer*, Bd. iv., 1854.

Blair Bell. (1) "Menstruation and its Relationship to the Calcium Metabolism," *Proc. Roy. Soc. Med.*, July 1908.

(2) "The Physiology of the Female Genital Organs," *Brit. Med. Journ.*, 13th March 1909.

Championnière. *Les lymphatiques utérines*, Paris, 1875.

Christ. "Das Verhalten der Uterusschleimhaut während der Menstruation," *Inaug. Diss.*, Giessen, 1892.

Cramer. "Transplantation menschlicher Ovarien," *Münch. med. Wochenschr.*, 1906.

Dahlgren and Kepner. *Principles of Histology*, Macmillan, 1908.

Ellerbroek. *Zentralb. f. Gyn.*, 1909.

Findley. "Anatomy of the Menstruating Uterus," *Amer. Journ. Obstet.*, vol. xlv., 1902.

Fraenkel. "Die Function des Corpus Luteum," *Archiv. f. Gyn.*, Bd. lxviii.

Frei. *Handbuch der Histol. und Histoch. des Menschen*, Leipzig, 1874.

Gebhard. (1) "Uber das Verhalten der Uterusschleimhaut bei der Menstruation," *Zeitschr. f. Geb. u. Gyn.*, Bd. xxxii.

(2) Veit's *Handbuch der Gyn.*, 1 Auflage, Bd. iii.

Heape. (1) "The Menstruation of Semnopithecus Entellus," *Proc. Roy. Soc.*, vol. liv., 1893.

(2) "The Menstruation and Ovulation of Monkeys and the Human Female," *Trans. Obstet. Soc.*, vol. xl., 1899.

Henle. *Handbuch der System. Anat. des Menschen*, Braunschweig, 1874.

Hennig. Quoted from Möricke.

Van Herwerden. "Bijdrage tot de Kennis von den menstrueelen Cyclus," *Tijdschrift d. Ned. Dierk. Vereen.*, vol. x., 1906.

Hitschmann and Adler. "Die Lehre von der Endometritis," *Zeitschr. f. Geb. u. Gyn.*, 1907, Bd. lx.

Hyrtl. Quoted from Möricke.

Janzer. "Untersuchungen der inneren Genitalien eines Kurz nach der Menstruation verstorbenen Mädchens," *Med. Annalen*, Bd. xiii., Heft 4, Heidelberg, 1848.

Johnstone. "Function and Pathology of the Reticular Tissue," *Amer. Gyn. and Obstet. Journ.*, vol. ix., 1896.

Johnstone. "The Menstrual Organ," *Brit. Gyn. Journ.*, Nov. 1886.

V. Kahlden. "Über das Verhalten der Uterusschleimhaut während und nach der Menstruation," Festschr. f. Hegar, *Beitrag. zur. Geb. u. Gyn.*, 1889.
Knauer. "Die Ovarien-Transplantation," *Archiv. f. Gyn.*, vol. lx., 1900.
Kölliker. Quoted from Möricke (*vide infra*).
Krause. *Allg. und Mikrosk. Anat.*, Hanover, 1876.
Kundrat und Engelmann. (1) "Untersuchungen über die Uterusschleimhaut," Stricker's *Med. Jahrbücher*, Wien., 1873.
(2) "Mucous Membrane of the Uterus," *Amer. Journ. of Obstet.*, vol. viii.
Leopold. (1) "Die Lymphgefässe des normalen nicht schwangeren Uterus," *Archiv. f. Gyn.*, Bd. vi.
(2) "Studium über die Uterusschleimhaut während der Menstruation," *Archiv. f. Gyn.*, Bd. xi., Heft 1.
(3) "Untersuchungen über Menstruation u. Ovulation," *Archiv. f. Gyn.*, 1885.
(4) *with* Mironoff. "Beitrag zur Lehre von der Menstruation u. Ovulation," *Archiv. f. Gyn.*, Bd. lxv., 1894.
Lipes. "Study of the Changes Occurring in the Endometrium during the Menstrual Cycle," *Albany Medical Annals*, vol. xxv., 1904.
Löhlein. "Das Verhalten der Uterusschleimhaut während der Menstruation," *Gyn. Tagesfragen*, Heft 2, Nr. 6, 1891.
Löwenhardt. "Die Berechnung und die Dauer der Schwangerschaft," *Archiv. f. Gyn.*, Bd. iii., 1872.
Löwenthal. "Eine neue Deutung des Menstruationprocess," *Archiv. f. Gyn.*, Bd. xxiv., 1884.
Marshall. (1) *Physiology of Reproduction*, Longmans, Green & Co., 1910.
(2) "The Œstrus Cycle in the Common Ferret," *Quart. Journ. Microscop. Science*, vol. xlviii., 1904.
Marshall and Jolly. (3) *Contributions to the Physiology of Mammalian Reproduction*, Part I; "The Œstrus Cycle in the Dog," *Phil. Trans.*, B., vol. cxcviii., 1905.
Martin. "The Physiology of Ovulation, Menstruation, and Fertilisation," Hirst's *Obstetrics*, vol. i., 1888.
Meckel. "Über die anatomischen Verhältnisse der Menstruation," *Jenaische Annalen f. Physiol. u. Med.*, Bd. i., 1850.
Minot. *Human Embryology*, 1892.
Möricke. "Die Uterusschleimhaut in den verschiedenen Altersperioden und zur Zeit der Menstruation," *Zeitschr. f. Geb. u. Geburts.*, Bd. vii., 1882.
Morris. (1) "The Ovarian Graft," *New York Med. Journ.*, 1895.
(2) "Case of Heteroplastic Ovarian Grafting Followed by Pregnancy," *New York Med. Journ.*, 1906.
Nagel. "Die weiblichen Geschlechtsorgane," Bardelaus' *Handbuch der Anatomie*, Jena, 1896.
Norris and Keene. "Changes in the Normal Endometrium during Menstrual Life," *Surgery, Gynecology, and Obstetrics*, Jan. 1910.
Pankow. *Archiv. f. Gyn.*, 1906 and 1909.
Plüger. *Bedeutung und Ursache der Menstruation, Untersuchungen aus dem physiol. Laboratorium zu Bonn*, Berlin, 1865.

Poirier. *Lymphatiques des organes génitaux de la femme*, Paris, 1890.

Pompe van Meerdervoort. "Die Gebärmutterschleimhaut in normalen Zustande und während der Menstruation," *Nederl. Tijsch. v. Verloosk en Gyn.*, Bd. vii., 1896.

Pouchet. Quoted from Mörieke (*vide supra*).

Robin. *Mémoires de l'académie impériale de médieine*, tome xxv., Paris.

Sigismund. "Ideen über das Wesen der Menstruation," *Berlin. klin. Woehenschr.*, No. 52, 1871.

de Sinéty. "Recherehes sur la muqueuse utérine pendant la menstruation," *Gazette médicale*, Paris, No. 7, 1881.

Strassmann. "Beiträge zur Lehre von der Ovulation, Menstruation, und Conception," *Archiv. f. Gyn.*, vol lii., 1896.

Tait. Quoted from Whitridge Williams (*vide infra*).

van Tussenbroek und Mendes de Leon. "Zur Pathologie der Uterus-Mukosa," *Archiv. f. Gyn.*, Bd. xlvii.

Underhill. "Note on the Uterine Mucous Membrane of a Woman who died immediately after Menstruation," *Edin. Med. Journ.*, August 1878.

Webster. *Human Placentation*, Chicago, 1900.

Wendeler. "Demonstration von mikroskopischen Präparaten zweier menstruierender Uteri," *Zeitschr. f. Geb. u. Gyn.*, Bd. xxxii., 1895.

Westphalen. "Zur Physiologie der Menstruation," *Archiv. f. Gyn.*, Bd. lii.

Williams (Sir John). "On the Structure of the Mucous Membrane of the Uterus and its Periodical Changes," *Obstet. Journ. of Great Britain and Ireland*, Nos. 23-4, 1875.

Williams (Whitridge). *Obstetrics*, 2nd ed., Appleton, 1908.

Wyder. "Das Verhalten der Mukosa Uteri während der Menstruation," *Zeitschr. f. Geb. u. Gyn.*, Bd. ix.

Pregnant Tube and Chorionepithelioma

Berkeley and Bonney. "Tubal Gestation: a Pathological Study," *Journ. Obstet. and Gyn. of Brit. Empire*, 1905.

Fellner. "Uber das Verhalten der Gefässe bei Eileiterschwangerschaft," *Archiv. f. Gyn.*, Bd. lxxiv., Heft 3.

Heinsius. "Uber die Beziehungen zwischen kindlichen und mütterlichen Elementen bei ektopischer Gravidität," *Zeitschr. f. Geb. u. Gyn.*, Bd. liv., Heft 1.

Kroemer. "Untersuchungen über die tubare Eieinbettung," *Archiv. f. Gyn.*, 1903, Bd. lxviii.

Marchand. "Uber das maligne Chorionepitheliom," *Zeitschr. f. Geb. u. Gyn.*, Bd. xxxix., 1898.

Raschkes. "Beitrag zur Frage der Graviditas Tubaria Interstitialis Propria," *Monatsschr. f. Gyn.*, Bd. xvii.

Schambacher. Uber wahre und vorgetäuschte Tubarschwangerschaft," *Zeitschr. f. Geb. u. Gyn.*, Bd. xlviii.

Teacher. (1) "On Chorionepithelioma," *Trans. Lond. Obstet. Soc.*, 1903, vol. xlv., and *Journ. Obstet. and Gyn. of Brit. Empire*. vol. iv., 1903.

(2) "On the Development and Natural Healing of Secondary

Tumours of Chorionepithelioma," *Journ. Path. and Bact.*, vol. xii., part iv., 1908.

Veit. "Uber Deportation der Chorionzotten," *Zeitsehr. f. Geb. u. Gyn.*, 1901, 466-504.

Wade and Watson. "Anatomy and Histology of an Early Tubal Gestation," *Trans. Obstet. Soe. Edin.*, 1907-1908.

Young. "Anatomy and Histology of the Pregnant Tube," *Trans. Obstet. Soc. Edin.*, 1908-1909, and *Edin. Med. Journ.*, August 1909.

Uterine Pregnancy and the Decidual Membrane

Bernard. "Sur une nouvelle fonetion du plaeenta," *C. R. Aead. Seie.*, Paris, vol. xlviii , 1859.

Bryee and Teaeher. *Early Development and Imbedding of the Human Ovum*, Maelehose, Glasgow, 1908.

Chipman. "Observations on the Plaeenta of the Rabbit," Laboratory Reports, Roy. Coll. Phys., Edinburgh, vol. viii., 1903.

Eden. *Proe. Roy. Soc., Lond.*, 1896.

Godet. *Dissert. inaug. à la faculté de médicine de Berne*, Neuveville, 1877.

Hubreeht. "Plaeentation of Erinaeeus Europæus," *Quart. Journ. Mic. Scienee*, vol. xxx., 1889.

Jung. *Beiträge zur frühesten Ei-Einbettung beim mensehliehen Weibe*, Berlin, 1908.

Kastsehenko. "Das mensehliehe Chorionepithel u. dessen Rolle bei d. Histogen. d. Plaeenta," *Archiv. f. Anat. u. Physiol., Anat. Abthlg.*, 1885.

Klein. "Entwiekelung und Rückbildung der Deeidua," *Zeitsehr. f. Geb. u. Gyn.*, Bd. xxii , 1891.

Leopold. *Ein sehr junges menschliches Ei*, Hirzel, Leipzig, 1906.

Loehhead. (1) *Trans. Obstet. Soe , Edin.*, vol. xxxiii., 1907-8.

(2) *Physiology of Reproduction*, Longmans, Green & Co., 1910, Artiele on "Fœtal Nutrition."

Marehand. *Beiträge zur Kenntniss der Placentarbildung*, Marburg, 1898.

Maximow. "Zur Kenntniss des feineren Baues der Kaninehen Plaeenta," *Archiv. f. Mikr. Anat*, Bd. li., 1897.

Merttens. "Beiträge z. normalen u. path. Anatomie der mensehlichen Plaeenta," *Zeitschr. f. Geb. u. Gyn.*, Bd. xxx., 1894.

Peters. *Die Einbettung des menschlichen Eies*, Deutieke, Wien, 1899.

Rossi-Doria. "Uber die Einbettung des mensehliehen Eies," *Archiv. f. Gyn.*, Bd. lxxvi., 1905.

V. Spee. (1) "Neue Beobachtungen über sehr frühe Entwickelungsstufen des mensehliehen Eies," *Archiv. f. Anat. u. Physiol., Anat. Abth.*, 1896.

(2) "Die Implantation des Meersehweinehen Eies," *Zeitschr. f. Morph. u. Antropol.*, Bd. iii., 1901.

(3) "Demonstration eines junges Stadium der menschliehen Eieinbettung," *Verh. d. deutschen Gesellsch. f. Gyn.*, vol. xi., 1906.

Stolper. *Monatsschr. f. Geb. u. Gyn* , vol. xxiv., 1906.

Webster. *Human Placentation*, Chieago, 1900.

Williams (Whitridge). *Obstetrics*, 2nd ed., 1908, Appleton.

Placental Ferments

Ascoli. "Passiert Eiweiss die placentare Scheidewand?" *Zeitschr. f. phys. Chemie*, vol. xxxvi., 1902.

Bergell und Liepmann. "Uber die in der Placenta enthaltenen Fermente," *Münch. med. Wochenschr.*, 1905.

Bottazzi. "Placental Activity," *Boll. della R. Accad. med. Genova*, vol. xviii.

Charrin et Goupil. "Physiologie du placenta," *Comp. rend. de l'Acad. des Sciences*, tomes cxli. and cxlii.

Lochhead. *Vide supra.*

Merletti. "Ricerche e studi interno ai poteri selettivi del' epithelio dei villi coriali," *Rass. d'ost e. ginec.*, 1903.

Savaré. "Zur Kenntniss der Fermente der Placenta," *Beiträge zur chem. physiol. u. path.*, Bd. ix., 1907.

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PLATE I.

Showing Structure of Uterine Mucosa.—The stroma consists of freely intercommunicating stellate cells, the spaces between which are expanded by the premenstrual œdematous escape. The walls of the expanded vessels are composed in places by flattened cells (*c*), in places by cells which are identical with the ordinary stroma elements (*f*). Note the free communications between the lining cells and the adjacent cells of the stroma. Where the vessel wall is cut tangentially the similarity between intima and stroma is well seen (*f*). In places (*d*, *g*) see detachment and displacement of the intima and stroma in the process of expansion. The red cells are escaping in places, but it is to be noted that, whereas the vessels are distended with blood, and the bounding cells are apparently widely separated, the blood leakage is occurring in only a few places.

PLATE I.

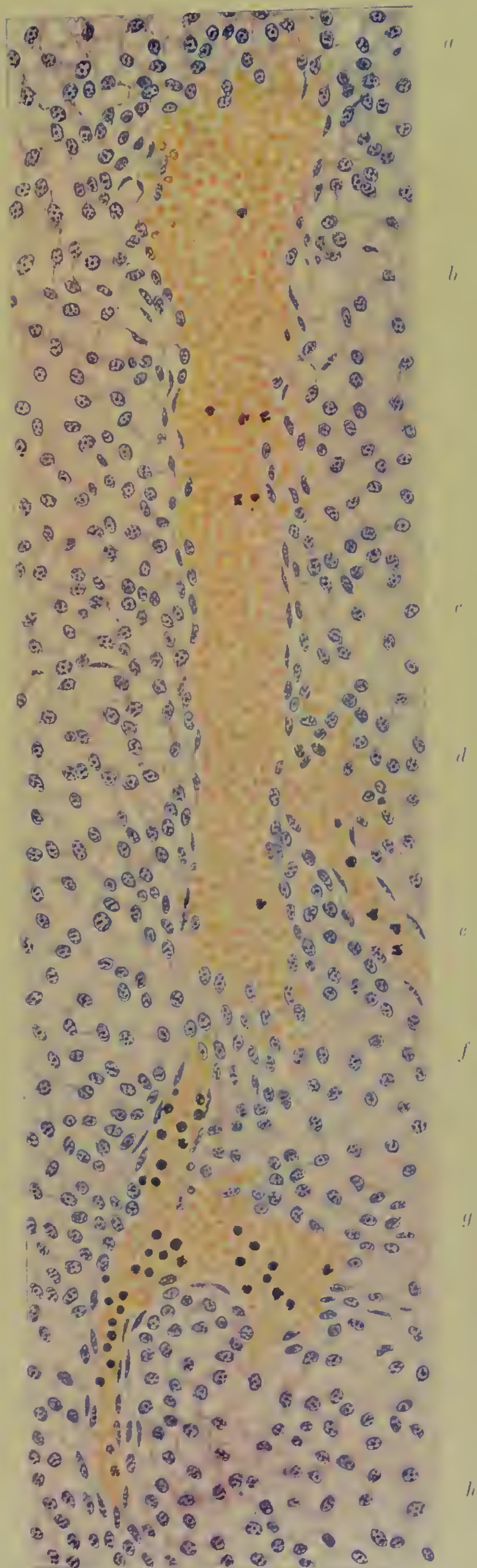


PLATE II.

Showing Structure of Vessel and Stroma (Menstrual).—See freely communicating stroma elements forming a homogeneous tissue. Expanded vessel or sinus bounded in places by flattened intima, in places by cells identical with surrounding stroma. Note communications between intima and stroma. Detachment and opening-out of intima and stroma in process of expansion.

PLATE II.

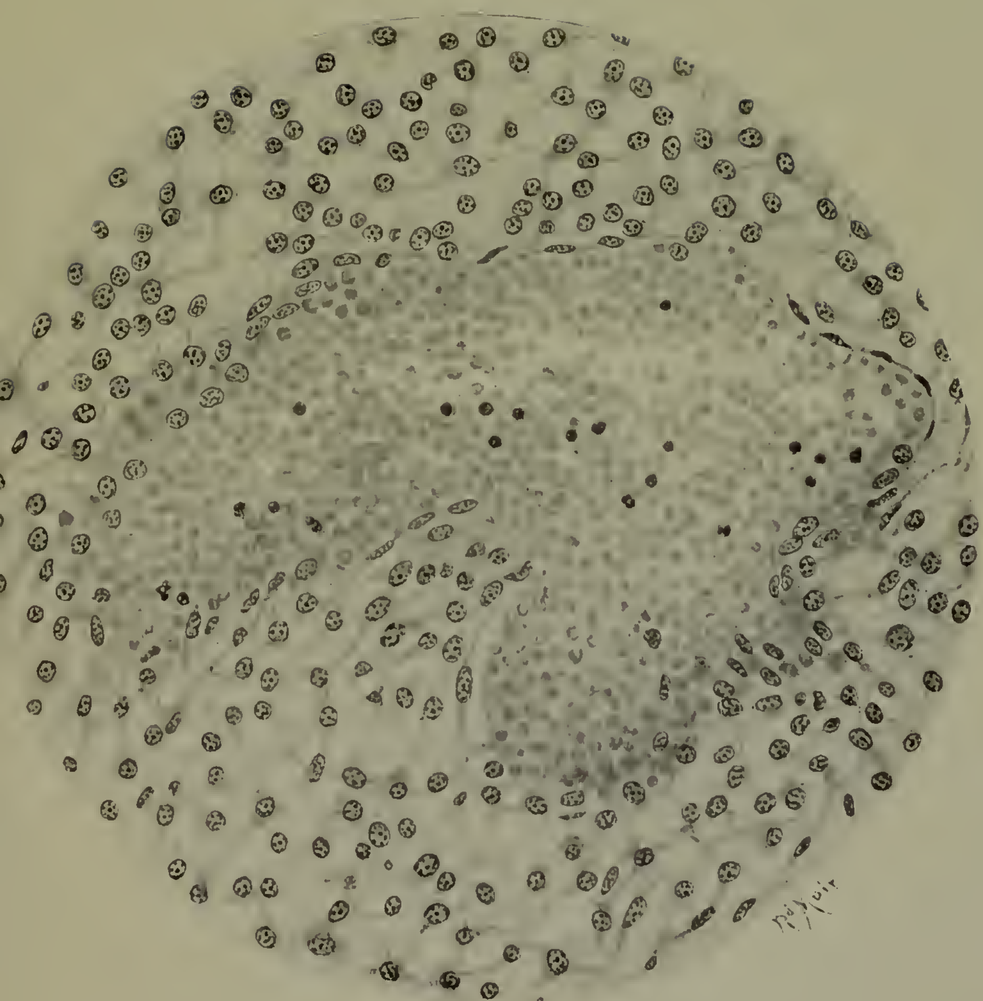


PLATE III.

Showing Structure of Stroma of the Uterine Mucosa and the Changes which occur in the Premenstrual Escape of Fluid from the Vessels (× 1000).—The tissue is opened out by blood fluid and there is some hæmorrhage. The intercellular spaces are expanded ; they are, in most places, enclosed by complete protoplasmic partitions. In addition, the stroma protoplasm is broken up by a multitude of fluid spaces of greatly varying sizes. The spaces again are separated from one another by protoplasmic partitions, and their formation has led to a marked swelling-up of the original "cells." The condition is clearly due to a fluid imbibition by the protoplasm, and the partitions are clearly sections of complete films which envelop the imbibed fluid. The change has involved the stroma uniformly, and indicates that this tissue consists of a homogeneous soft protoplasm. It is seen that the so-called network corresponds to the appearance given by a section across the protoplasmic films. In lower part see fine vessel, whose wall is formed by elements structurally identical with the surrounding stroma. Here, again, see evidence of fluid imbibition, which is leading to a teasing-out of the wall. Note the displacement of the protoplasm on the inner aspect which follows the imbibition — this is clearly leading to an expansion of the vessel lumen.

PLATE III.

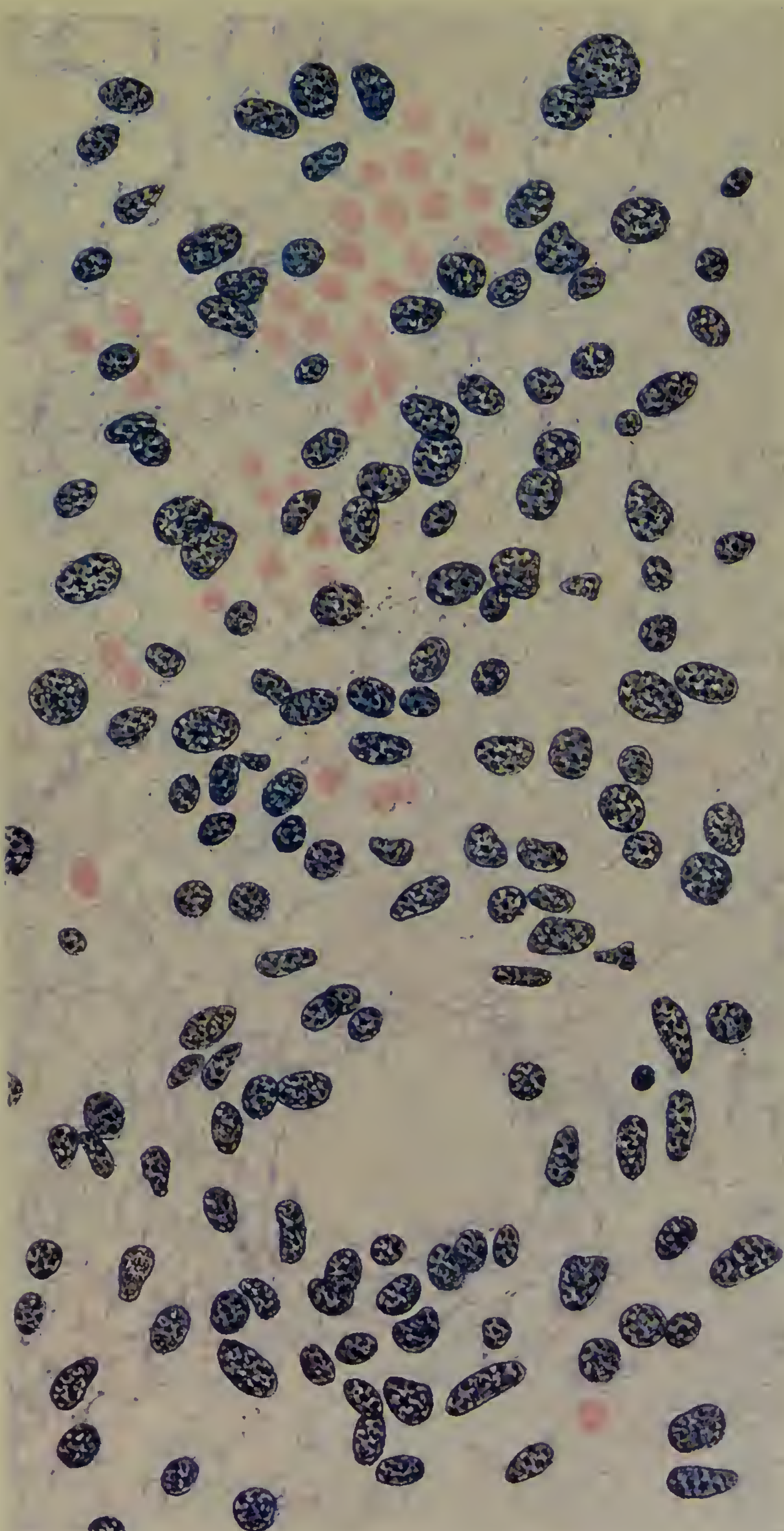


PLATE IV.

Showing Structure of Stroma and Cause of Escape of Blood Fluid ($\times$ 1000).—The intercellular spaces are enlarged ; they are bounded all round by protoplasmic partitions. In many places see perinuclear protoplasm beset with fluid spaces with an enlargement of the original "cells." The network of other writers is seen to consist, not of fibrils, but of the fine films separating the fluid chambers. On section they give, at first sight, the impression of being protoplasmic threads.

PLATE IV.

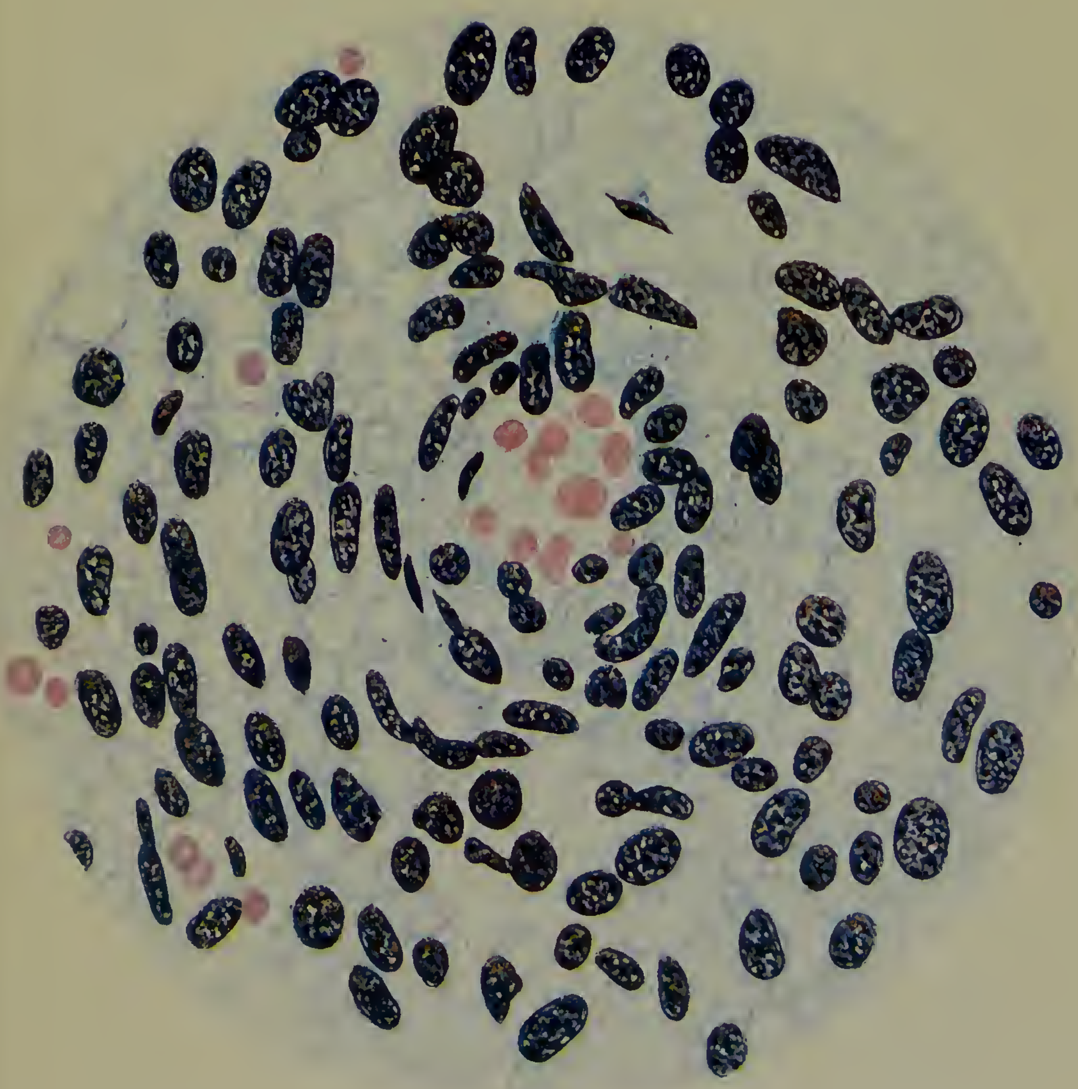


PLATE V.

Tubal Pregnancy.—In lower part see portion of intervillous space with chorionic villi. Above this to the right see the remains of the epithelial mucous lining of the tubal lumen. To the left see marked hæmorrhagic escape. This is seen to be occurring all round a vessel before the chorionic cells have reached it, and is found at some distance in the tubal wall. There is also, as is often present, an oozing from the vessels on the peritoneal aspect of the tube. The remainder of the tubal wall is œdematous. Several expanded blood sinuses are seen.

PLATE V.

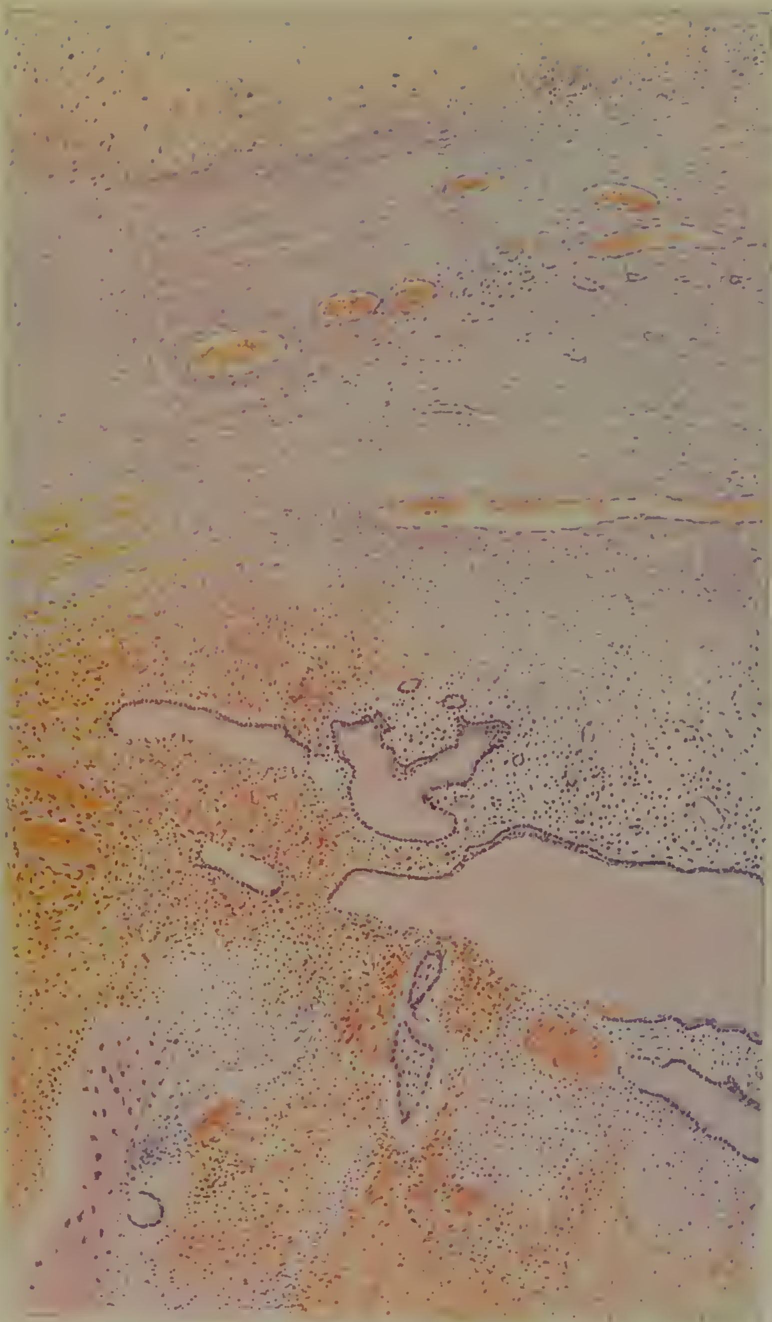


PLATE VI.

Tubal Pregnancy.—Vessel in tubal wall in the degenerating zone, but still at some distance from the chorionic cells. Note the swelling up and projection into the lumen of the intimal cells as the result of a fluid imbibition. The surrounding tissues are spread apart with fluid which has accumulated in spaces of greatly different sizes. The appearances are somewhat similar to those present in Plates III. and IV.

PLATE VI.

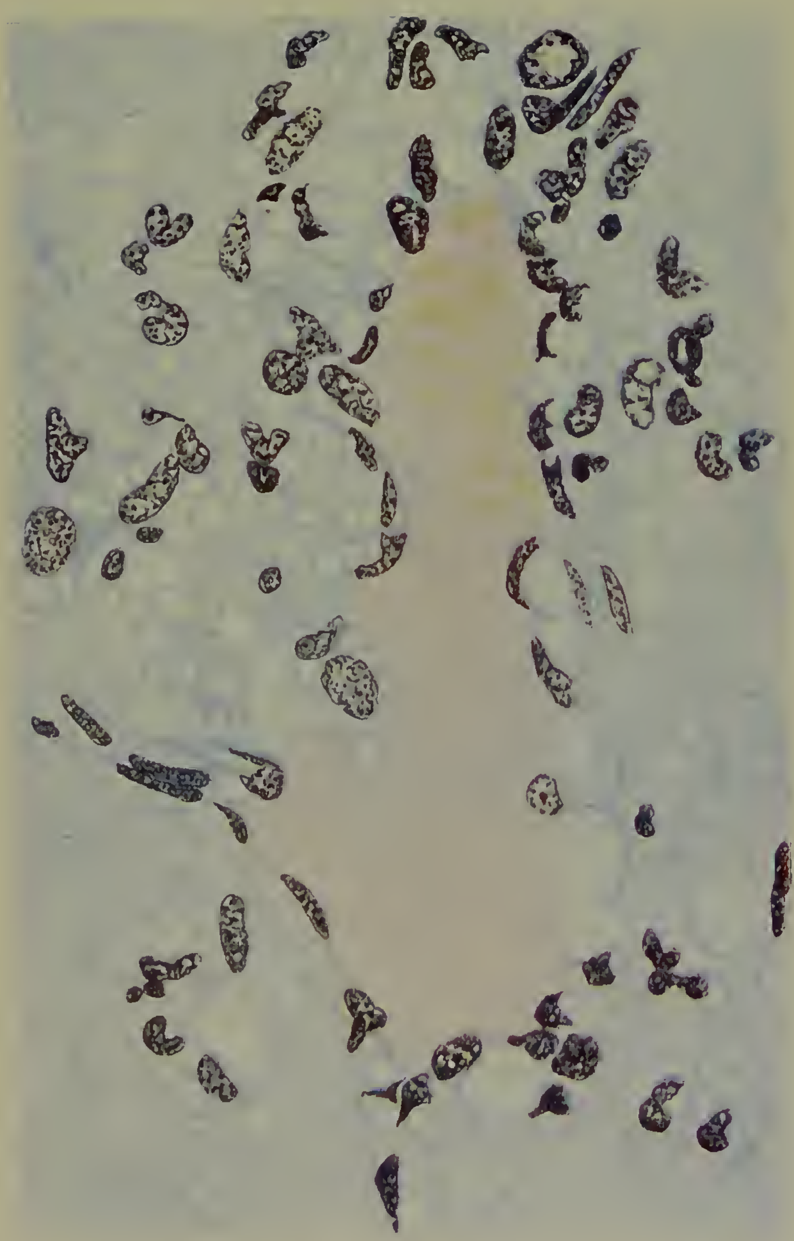


PLATE VII.

TUBAL PREGNANCY.—Portion of wall of tube at long distance from the chorionic cells. To the left an expanded fine-walled vessel or sinus is shown. On lower wall evidence of imbibition by the intimal cells is seen. To the right side the manner in which the vessel expands is shown ; the disappearance or displacement of the fine film of cell-protoplasm as a result of the fluid imbibition will carry the blood-space a corresponding degree outwards (*cf.* Plate III.). Note the widespread imbibition by the connective-tissue elements. In several places the manner of formation of the œdematous tracks is seen — the appearances suggest that these are produced by an amalgamation of the fluid spaces formed by the imbibition process, *i.e.* in a manner similar to that by which the sinuses expand. To the right side of the sinus there is a fluid space almost embraced by the expanding lumen.

Round the sinus wall there is evidence of a new-vessel formation. To the right side an elongated capillary track is seen. This is formed by an amalgamation of the intracellular fluid tracks formed in the intima by the imbibition with those formed in the connective-tissue cells—that is, into the wall of the expanding sinus and into the newly formed capillaries the connective-tissue elements are seen to be incorporated.

PLATE VII.

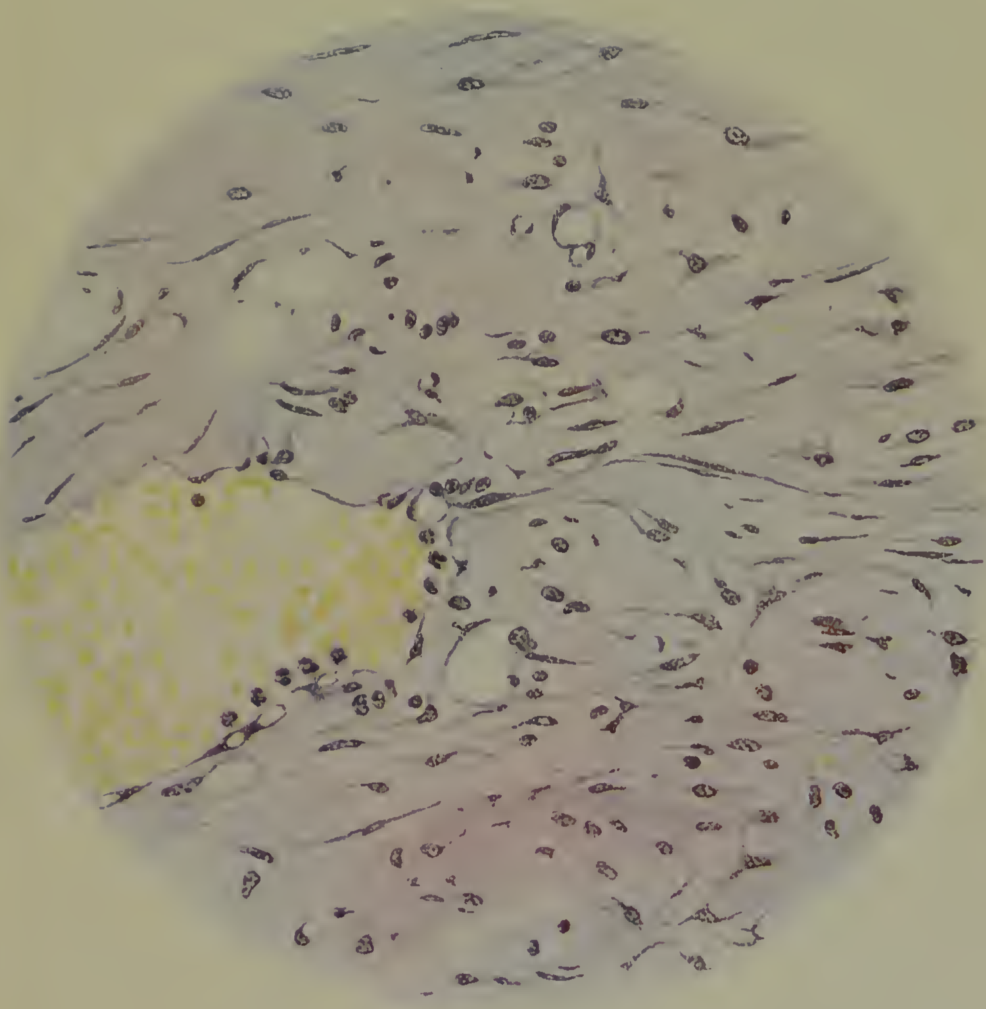


PLATE VIII.

Tubal Pregnancy.—Portion of tubal wall at long distance from chorionic elements, showing changes in intimal and connective tissue cells and the mode of expansion of the blood sinuses. Note the marked fluid imbibition by the cells, leading to the formation of intracellular fluid spaces, rounded, oval, or elongate on section. To the left side of the sinus the mode of expansion is seen ; the displacement or disappearance of the fine protoplasmic films results in a carrying out of the lumen. The mode of formation of the new capillaries is also indicated.

PLATE VIII.

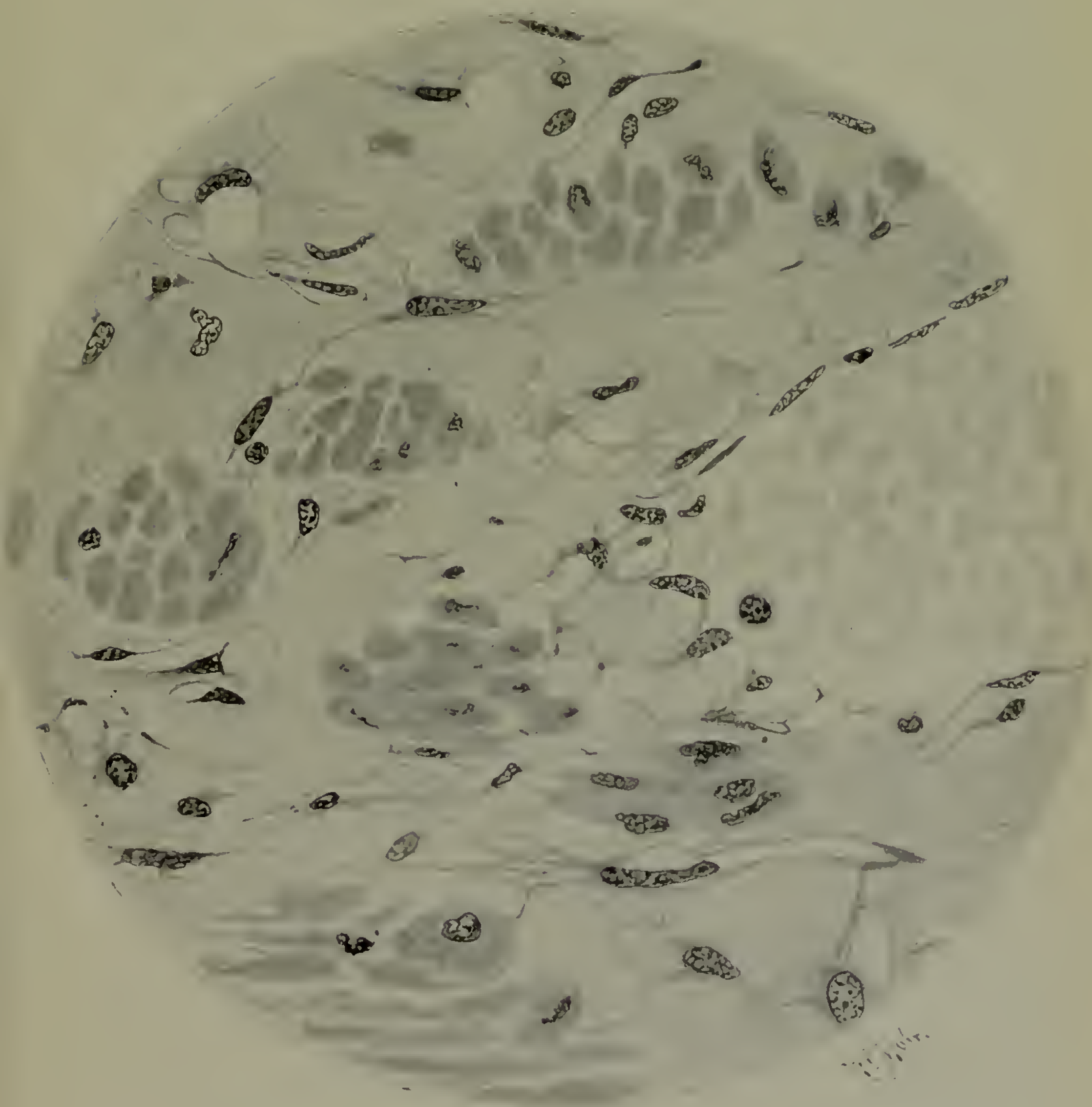


PLATE IX.

Tubal Pregnancy.—Section through part of tubal wall at long distance from the ovum. In the lower part see muscular coat which exhibits a marked œdematous and hæmorrhagic infiltration. This is especially evident round the thick-walled vein, the supporting coats of which are being detached in a wholesale manner by the escaping fluid. Round the greater part of its circumference the vessel is completely isolated from the muscular tissue of the tube by the fluid and blood. These changes are dependent on the chorionic biochemical materials. In the upper part see the mucous ridges of the tubal lining, the connective-tissue cells of which have undergone a decidual change. Here there is a complete absence of the œdematous tearing-up which is present throughout the muscular coat.

PLATE IX.

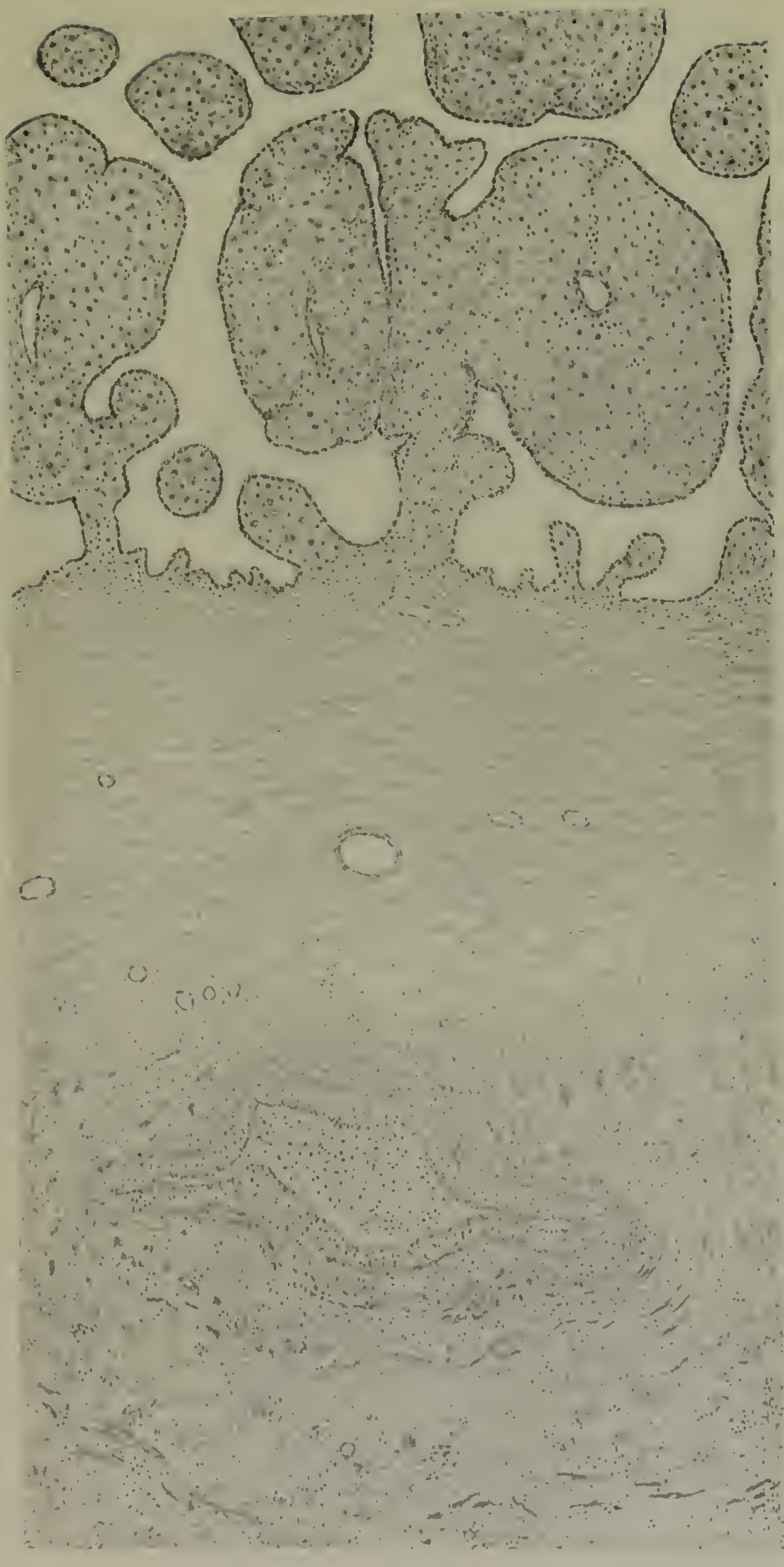


PLATE X.

CHORIONEPITHELIOMA.—Portion of muscular wall of uterus. In upper part see mass of chorionic cells invading the œdematous and degenerating maternal tissues. Below this a fine vessel is seen surrounded by a copious hæmorrhage. It will be noted that the blood exodus has occurred through apparently intact walls, and that there are no chorionic cells in the immediate proximity. In the thicker vessel in the lower part of the field see distinct evidence of a fluid imbibition. The wall throughout its entire thickness has become opened out by the formation of clear spaces, which have led to a marked bulging of the inner aspect of the wall into the lumen. Note in places the evidence of a new-vessel formation, especially near the chorionic cells.

PLATE X.

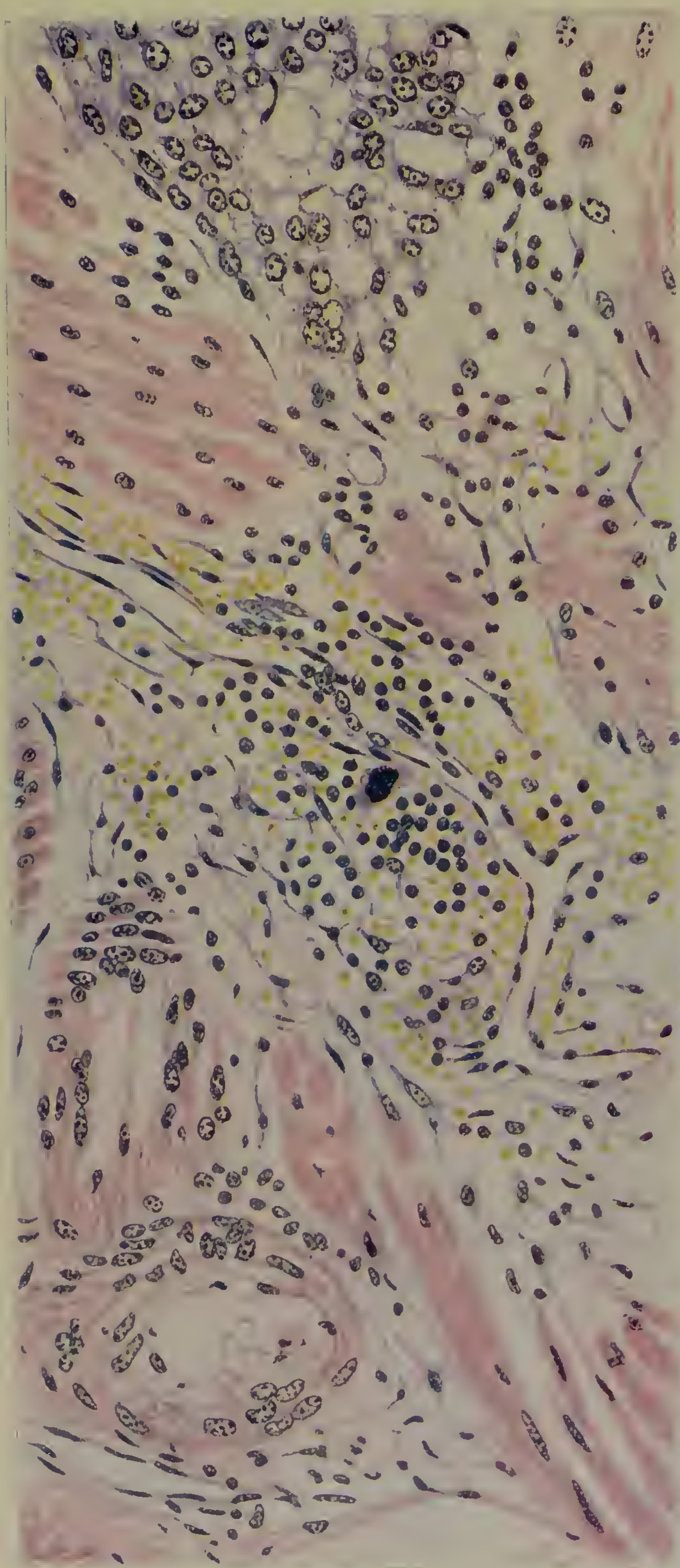


PLATE XI.

Chorionepithelioma.—Portion of muscular coat of uterus. To the right see clump of tumour cells in a blood space. Above and to the left side see manner in which the vessel walls become opened out in advance of the chorionic cells — note the spreading apart of the tissues by the fluid spaces. Below, see evidence of intimal imbibition. The tissues in general are the seat of a marked œdema.

PLATE XI.

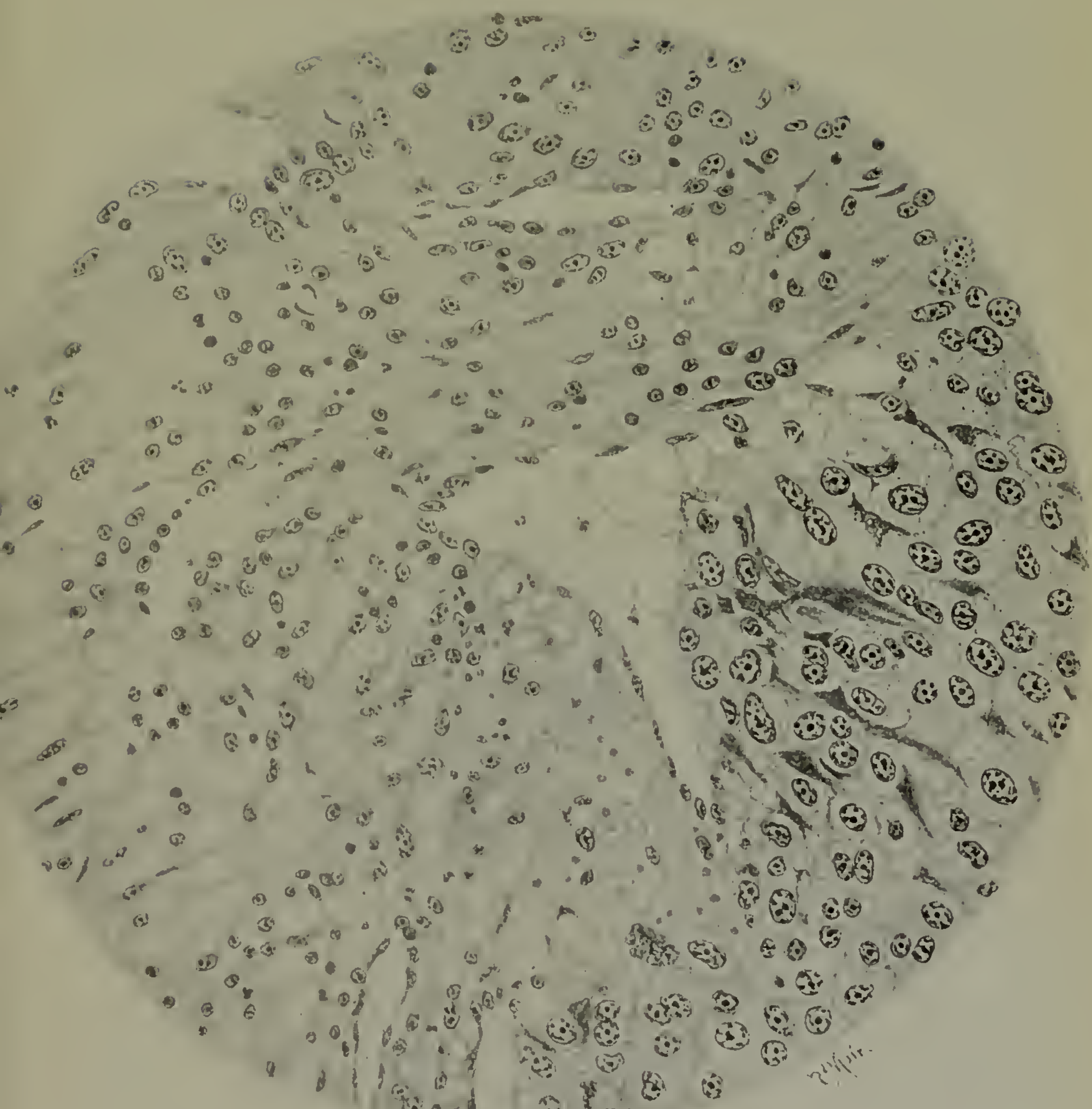


PLATE XII.

Chorionepithelioma.—Vessels in the uterine wall at a distance from the chorionic cells. Note the teasing-out and swelling of the walls by the clear fluid spaces with distinct evidence of imbibition. In places the red cells are being dragged out. The surrounding tissues are markedly œdematous. Several distended fine-walled blood or lymphatic vessels are present.

PLATE XII.

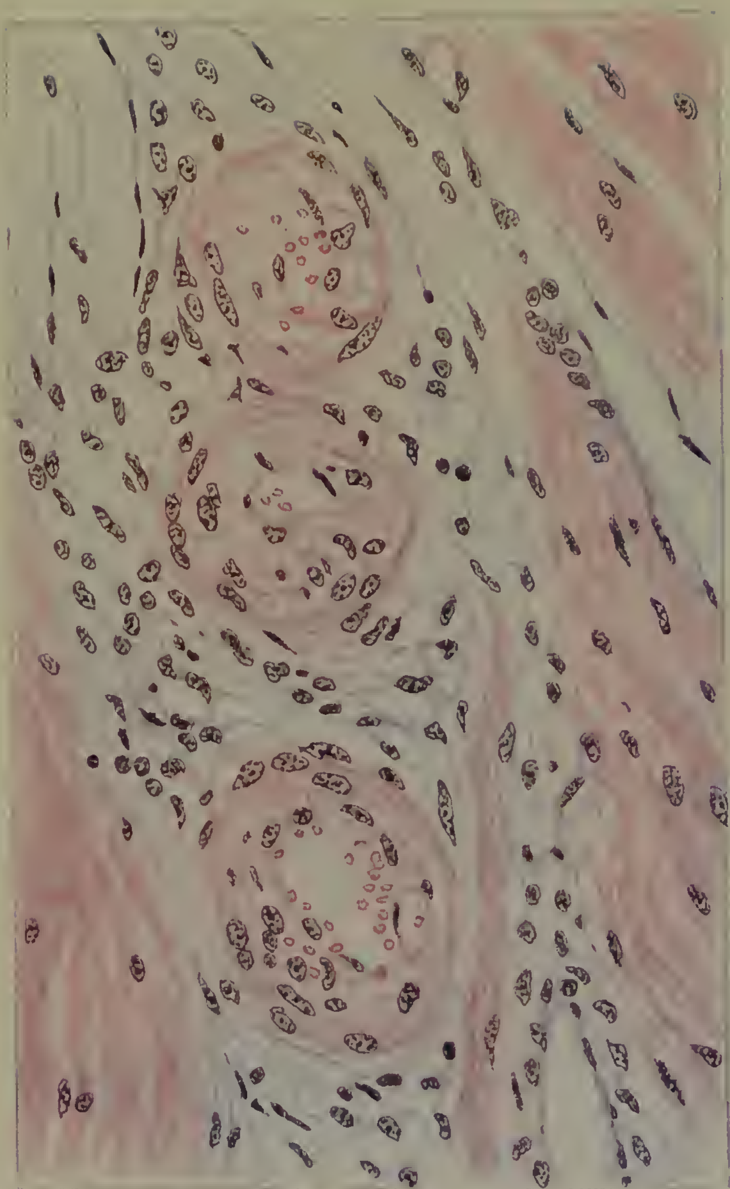


PLATE XIII.

Chorionepithelioma.—Section of uterine wall at a small distance from the chorionic cells showing changes which occur in the muscular elements ($\times$ 1000). Various phases in the disintegrative process are seen. The fibres swell up, often to many times their original size. This is seen in many cases to be dependent on the formation in the substance of the fibres of clear fluid spaces which lead to the displacement and swelling. The condition at first sight suggests a fatty degeneration. In many places the fibres are becoming broken up, and in places are seen to be gradually disappearing, apparently entering into a state of solution. The nuclei are degenerating.

PLATE XIII.

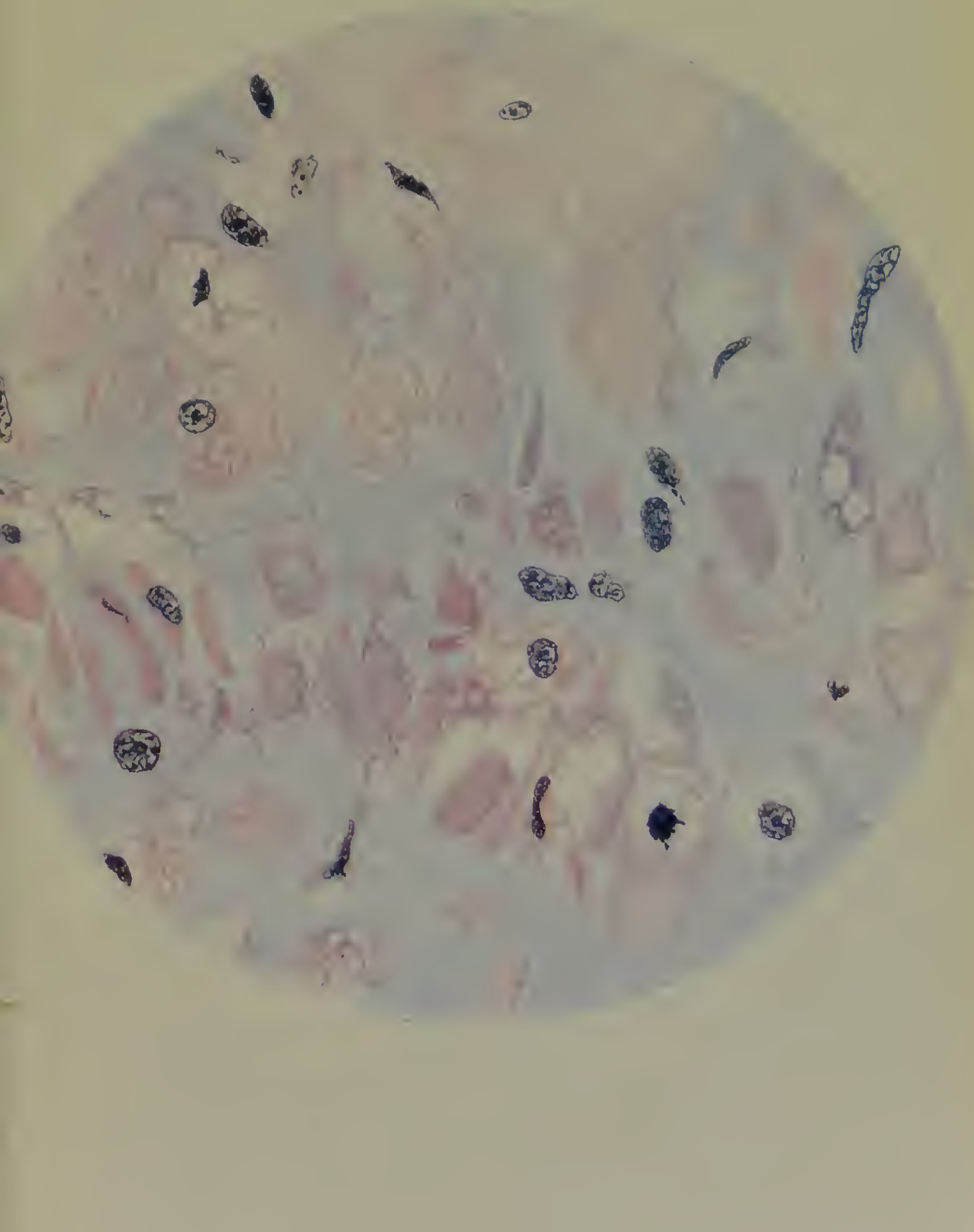


PLATE XIV.

Early Human Ovum ($\times 65$).—Section through the base of the "decidual lobule" of the mucosa more or less parallel to the surface, showing the implantation chamber with the early ovum lying immersed in the maternal blood. The ovum consists of a small elongate blastocyst, the surface of which has thrown out a number of rudimentary villi. It is invested by a uniform layer of epithelium (cytotrophoblast), with here and there masses of syncytium (plasmoditrophoblast) that seem to be detached in places. Note in some regions the solid strands of epithelium separating two neighbouring mesodermic villous stalks. The mesoderm fills the blastocyst and there is no trace of an embryo. The blood cavity is considerably larger than the ovum, and at one pole is separated from the surface only by a thin layer of tissue. It is bounded by the necrotic lamina of the mucosa. The mucous membrane for some distance from the ovum is markedly opened out by œdema and hæmorrhage and the vessels are expanded.

PLATE XIV.

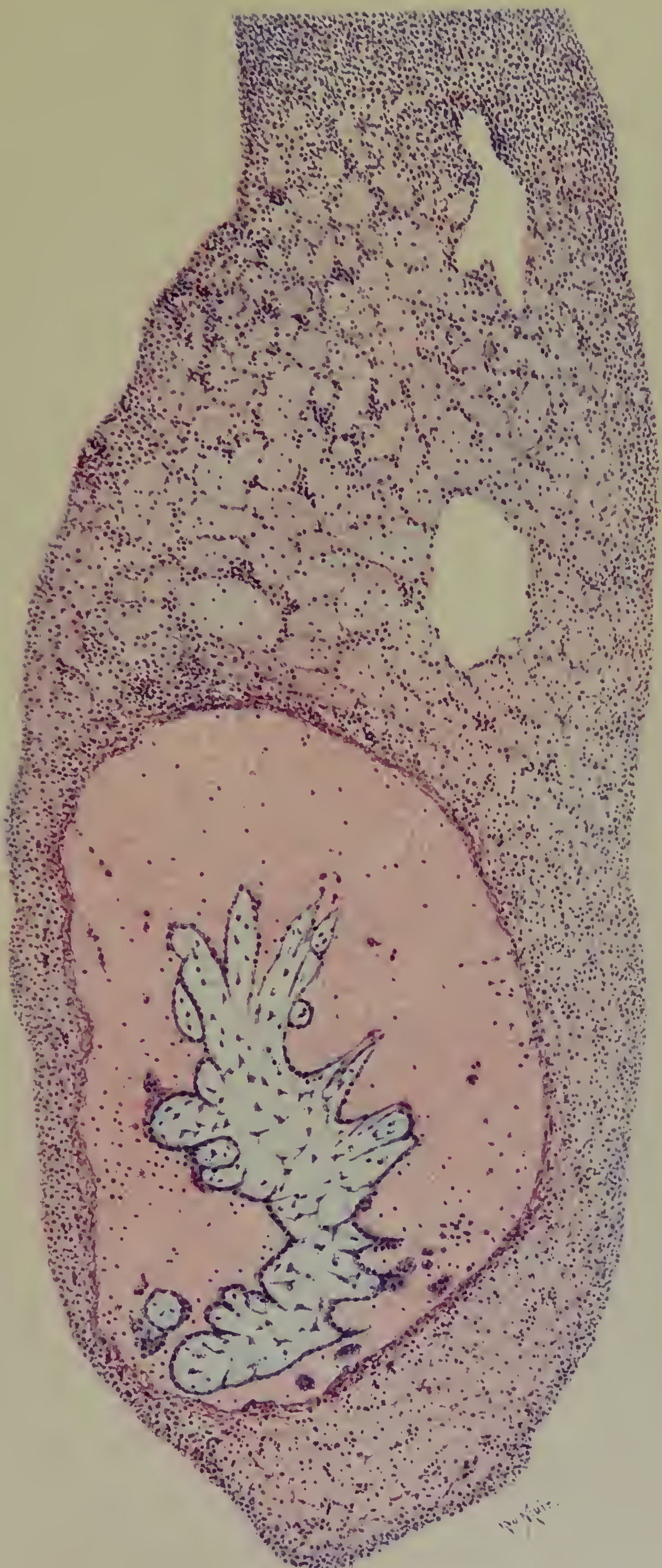


PLATE XV.

Early Human Ovum ($\times 75$).—Serial section through the "decidual lobule" approximately parallel to the surface of the mucosa and at a more superficial level than is represented in Plate XV. Here the outer pole of the blastocyst, devoid of villi, is in direct relation to the uterine lumen. The edges of the opening in the roof of the chamber are seen to extend only so far over the smooth rounded surface of the blastocyst. The rudimentary villi are seen, and at the innermost pole a part of the ovum is in the section separate from the main part because of the different planes in which the two poles of the blastocyst lie. The darkly staining necrotic lamina is well seen. Towards the lower and right side a mass of plasmodium is lying apparently free in a bay formed in the wall of the blood chamber. The spreading apart of the *Umlagerungszone* is well shown.

PLATE XV.

PLATE XVI.

Early Human Ovum ($\times 75$).—Serial section through the "decidual lobule" at a still more superficial level. The outer pole of the blastocyst is seen to project through the roof of the blood chamber. Only the surface in relation to the blood has retained its epithelial covering. This part of the blastocyst seems to be almost cut off from the main part of the blood cavity by the two decidual beaks. Between these there is still a narrow strait. The apparent thickening of the darkly staining necrotic tissue in this region is due to the obliquity of the section. In the main blood space a small part of the surface of the inner part of the blastocyst is cut tangentially. Note the masses of chorionic cells radiating from this. The necrotic lamina and the changes in the surrounding mucosa are again well shown.

PLATE XVI.

PLATE XVII.

Early Human Ovum.—Serial section through the "decidual lobule" at a still more superficial level than in Plates XIV.-XVI. The sections (which are all reproduced on the same scale, *i.e.* ×75 diameters) are seen to become smaller as they are followed towards the surface of the lobule. The outer pole of the ovum is projecting distinctly into the uterine cavity and is seen to be apparently shut off from the main blood cavity. This section in reality corresponds to the margin of the opening in the roof of the cavity. The inner part of the blood space is smaller, and contains in the centre a mass of the chorionic cells corresponding to the surface of the blastocyst. Note the strands detached from the necrotic lamina.

PLATE XVII.

PLATE XVIII.

Early Human Ovum.—Serial section near the surface of the "decidual lobule" (× 75). This section is carried across beyond the blood cavity. The teasing-out of the stroma of the mucosa is well shown. In the lower part is seen the outer pole of the blastocyst, which seems to be completely detached from the mucosa. This is in reality due to the fact that this part of the ovum overlaps the surface of the decidual lobule. The darkly staining material is not epithelium but a part of the necrotic layer of the mucosa ; it is covered by a cap of the paler-staining stroma.

PLATE XVIII.

PLATE XIX.

Early Ovum.—Section through the mucosa in the immediate proximity of the ovum ($\times$ 1000). Above is seen the blood cavity bounded by the necrotic lamina. A degenerating cell (maternal) is seen. Note especially the changes in the stroma protoplasm. The "cells" have become swollen, some in a truly decidual fashion. The preponderating change, however, is seen to be a displacement of the protoplasm by the formation of an immense number of clear spaces of greatly differing sizes. The perinuclear protoplasm is involved in the process which is due to a widespread imbibition of fluid. Into the spaces formed red cells have passed. Between the "cells" there is the so-called network, which is seen to consist in reality of the fine protoplasmic films separating the fluid chambers. Scattered about degenerating stroma cells are seen. Similar changes are present during menstruation (*see* Plates III. and IV.).

PLATE XIX.

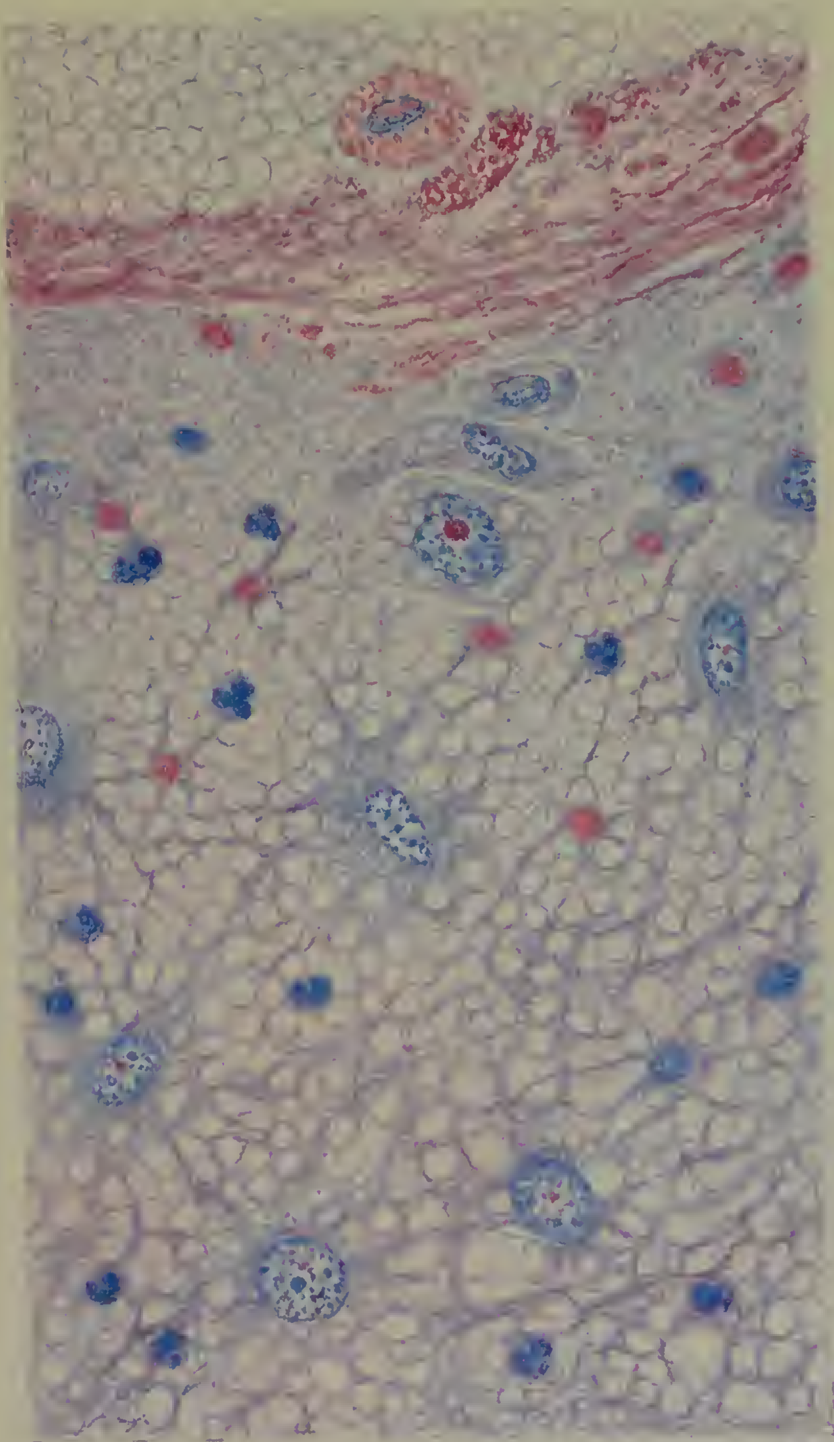
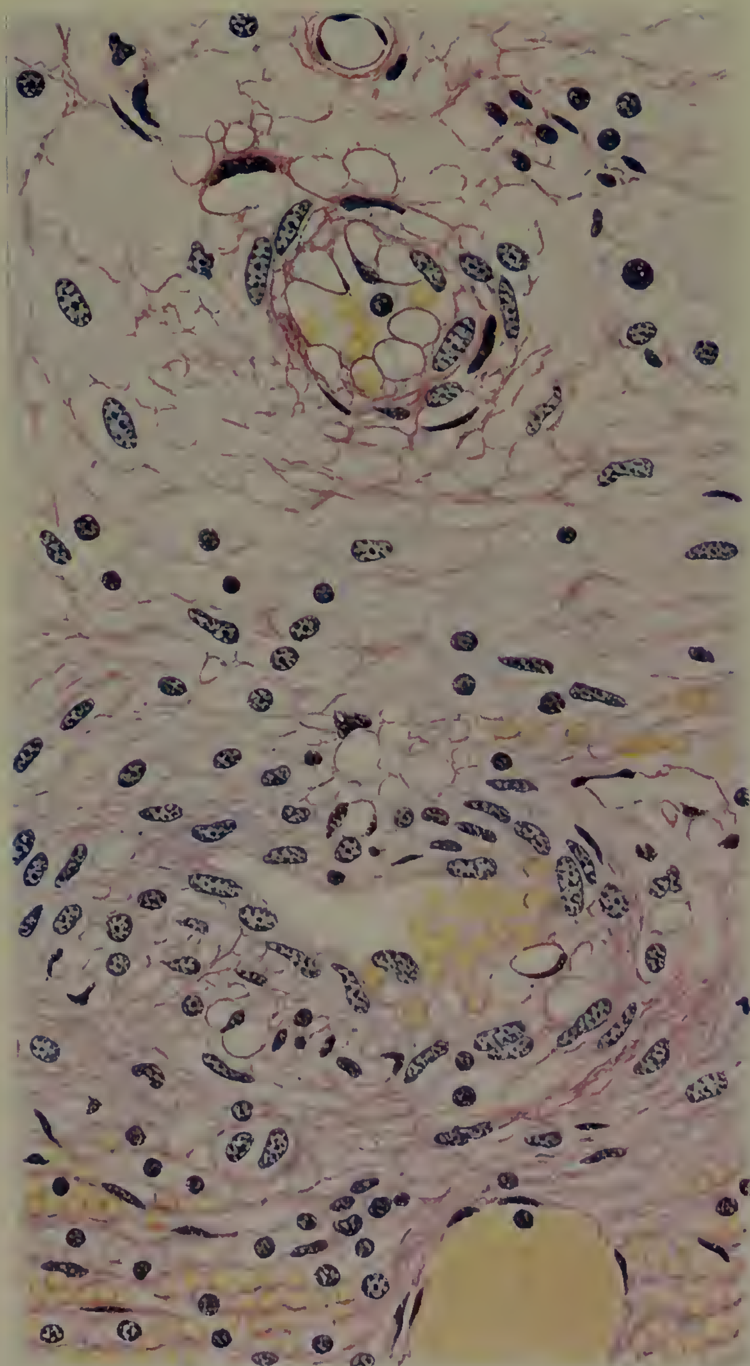


PLATE XX.

Early Human Ovum (lent by Dr. Teacher).—Section from the decidua at a small distance from an ovum approximately 17 or 18 days old. In the upper part a small vessel is seen with an œdematous opening-out of its walls. Note the distinct evidence of fluid imbibition by the intimal elements. In two places a red cell has been drawn into the vessel wall with the escaping fluid. Round the vessel the so-called network is seen. The changes in a cell immediately to the left upper aspect of the vessel reveal the real nature of this network. In the thick vessel under this a similar fluid accumulation in the wall is seen, and in places the red cells are being drawn out. In several places the spaces formed by the imbibed fluid correspond to newly produced capillary vessels. In the lower region of the plate part of a large fine-walled vessel or "distended capillary" is seen, through the walls of which there is occurring a copious hæmorrhage.

PLATE XX.



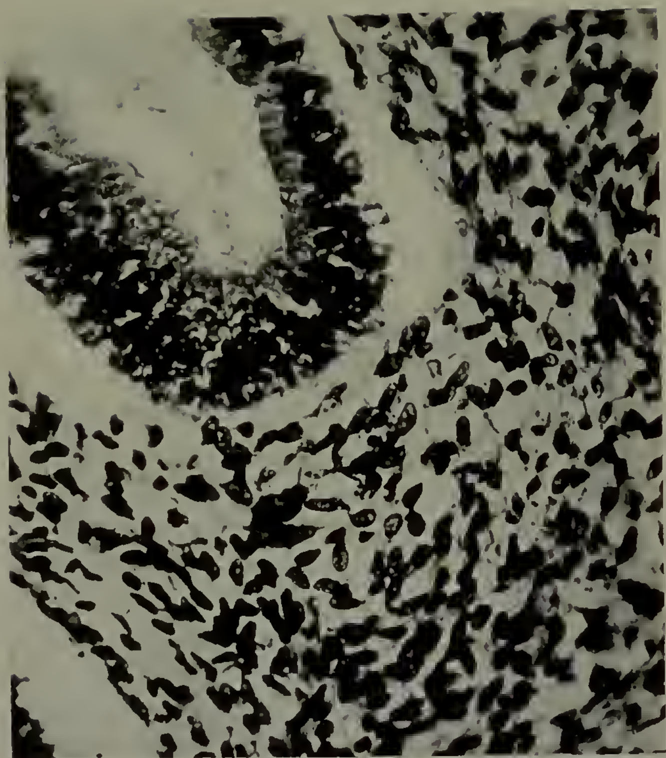


FIG. 1.—Portion of gland and stroma of uterine mucosa. This consists of mass of closely apposed branching "cells" united with one another. Gland has shrunk away from surrounding stroma. No evidence of basement membrane.

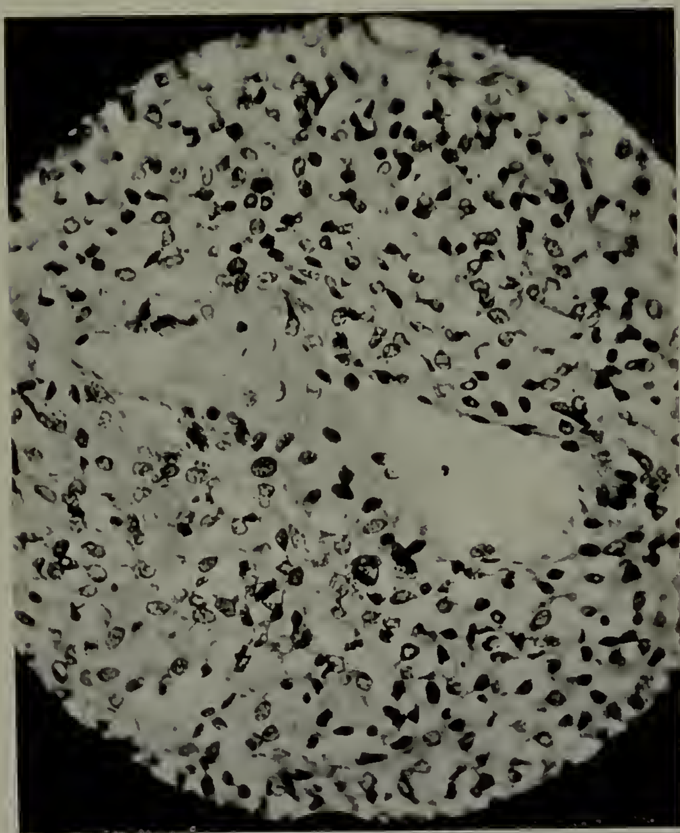


Fig. 2.—Stroma of uterine mucosa with blood sinus. Note structure of stroma—consists of uniform mass of protoplasm imperfectly differentiated into cells. Wall of sinus (lining layer cut tangentially in one part) formed by this same tissue.

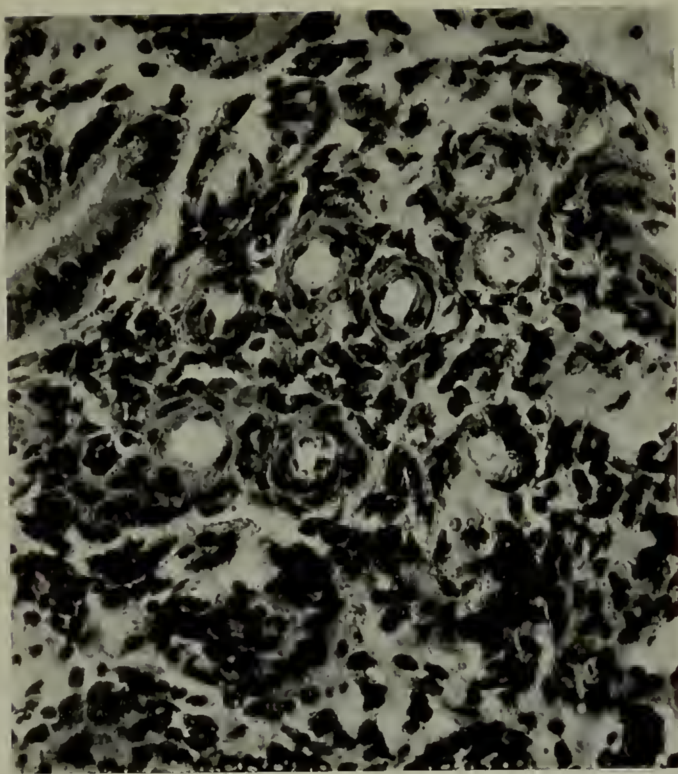


Fig. 3.—Resting stroma of uterine mucosa with bunch of blood-vessels. Note concentric arrangement of elements forming their wall.

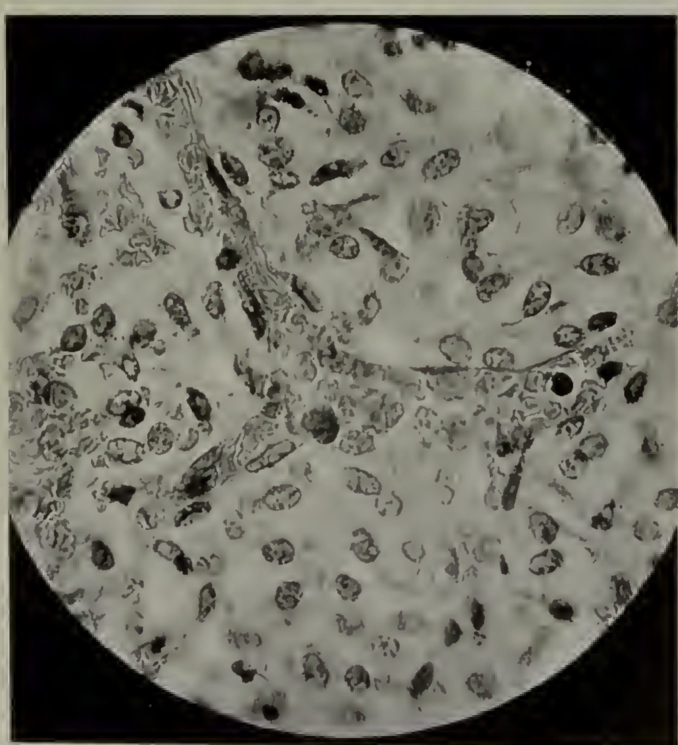


Fig. 4.—Stroma of uterine mucosa with fine vessel showing diapedesis of red cells (premenstrual).

FIG. 5. Stroma of uterine mucosa with two vessels; the upper has a flattened intima, the lower has wall throughout formed of elements similar to those of stroma.

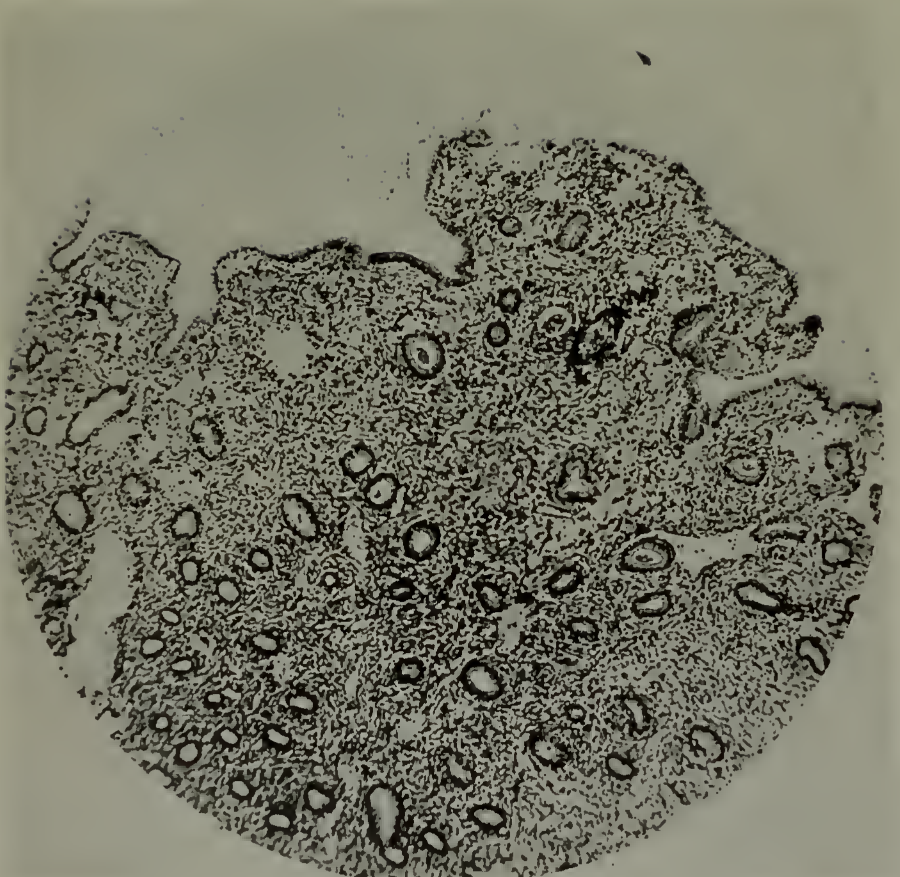


FIG. 6.—Menstruation (3rd day). Showing opening out of superficial strata of mucosa, with formation of spaces and sinuses. Surface folded, and at one part epithelium shed; otherwise well-retained.

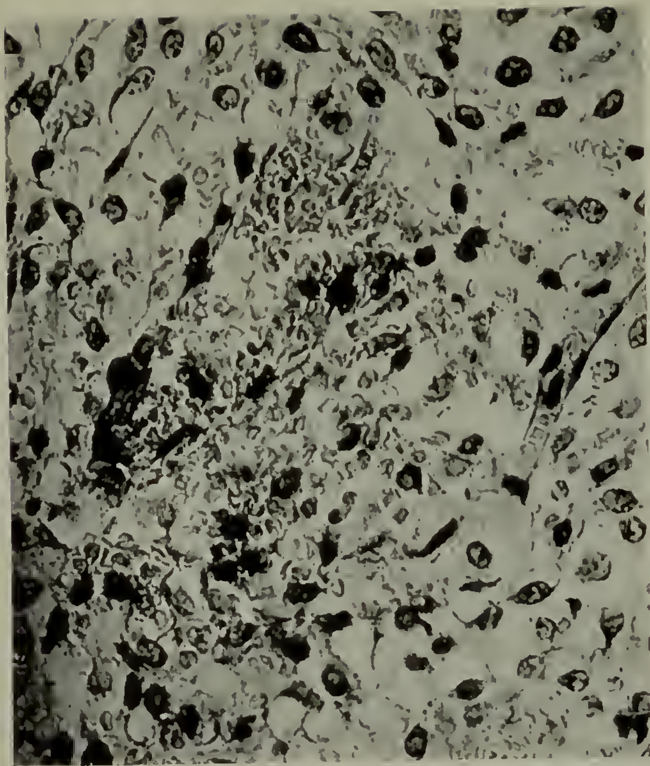


FIG. 7.—Uterine mucosa showing diapedesis of red blood corpuscles (premenstrual).

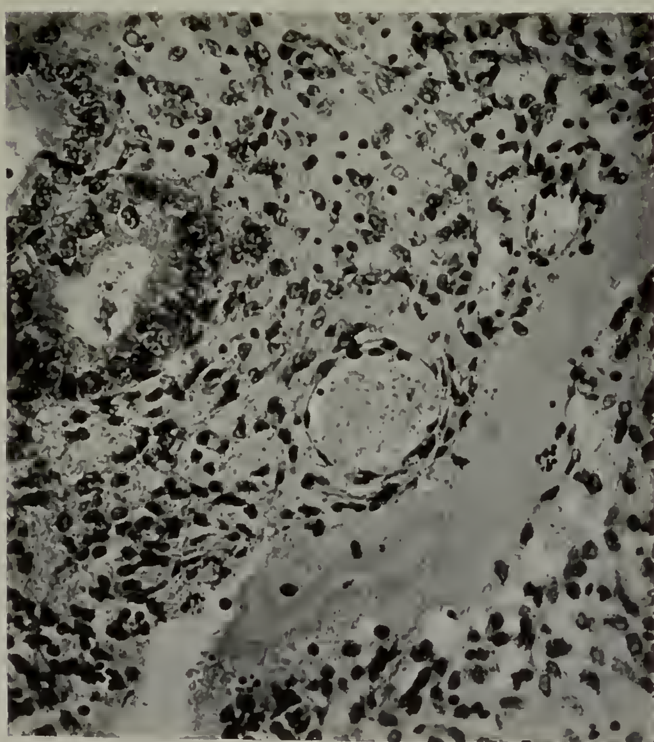


FIG. 8.—Uterine mucosa. Showing opening out of vessel wall by detachment of surrounding supporting layers. Marked hæmorrhagic escape (menstruation).

FIG. 9.—Stroma of uterine mucosa with vessel. Note structure of vessel wall and of the surrounding stroma.

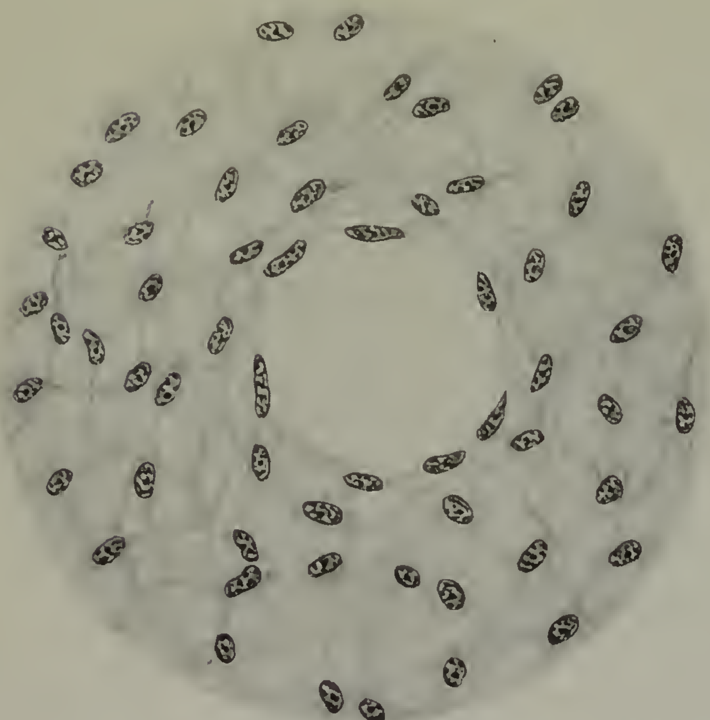


FIG. 10.—Stroma of uterine mucosa opened out by an œdematous exudate. Note separation of "cells," and the rich anastomotic connections between the neighbouring elements. The vessel is becoming expanded. This figure corresponds to a slightly later phase of the process than that in Fig. 9 (premenstrual).

FIG. 11. Opening out of stroma and vessel-wall at a still later phase. Note free connection between intima and stroma elements. The vascular expansion is occurring by a stepping back of the intima and into the new lining layer the stroma is incorporated.

FIG. 12.—Still later stage of œdematous exudate and of vascular expansion. Shows incorporation of stroma elements as new intima and evidence of new vessel budding.

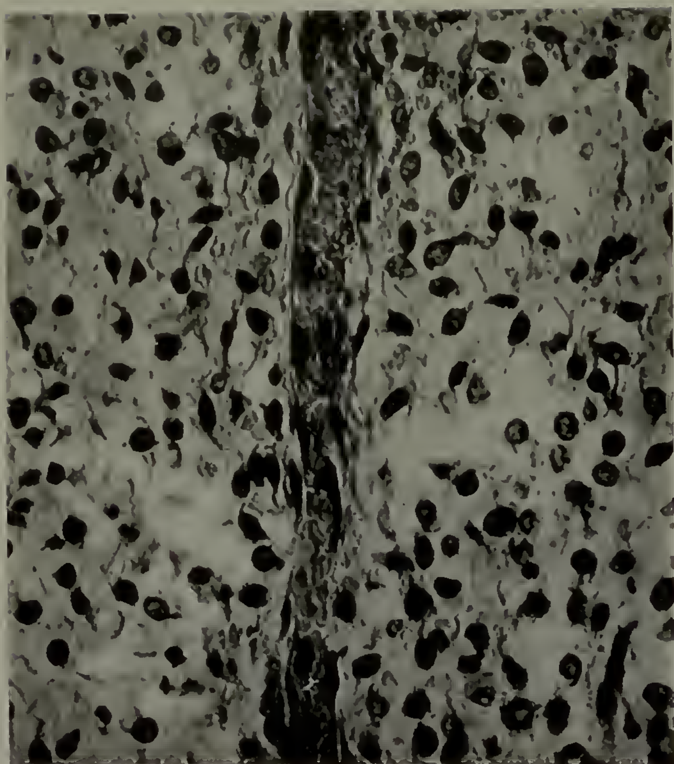


Fig. 13.—Straight vessel in œdematous (menstrual) stroma.

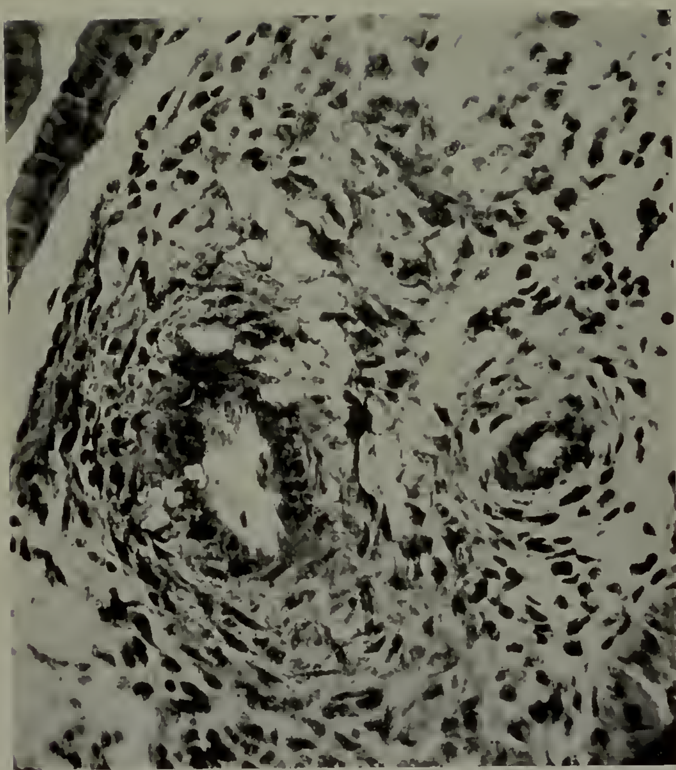


FIG. 14.—Thickened vessels in menstruating mucosa. Opening out of vessel wall in two places by œdematous tracks which pass into the surrounding opened-out stroma. On left side track passes continuously from intima to stroma except for presence of fine interrupting protoplasmic processes. Note detachment of supporting elements in concentric layers in vessel to right.

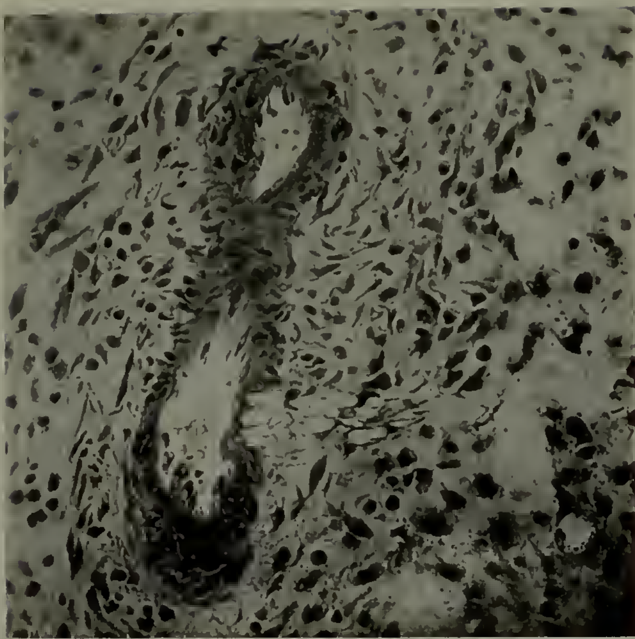


Fig. 15.—Thickened vessel in menstruating mucosa, with opening out by œdematous track on right side. Note changes in intimal elements.

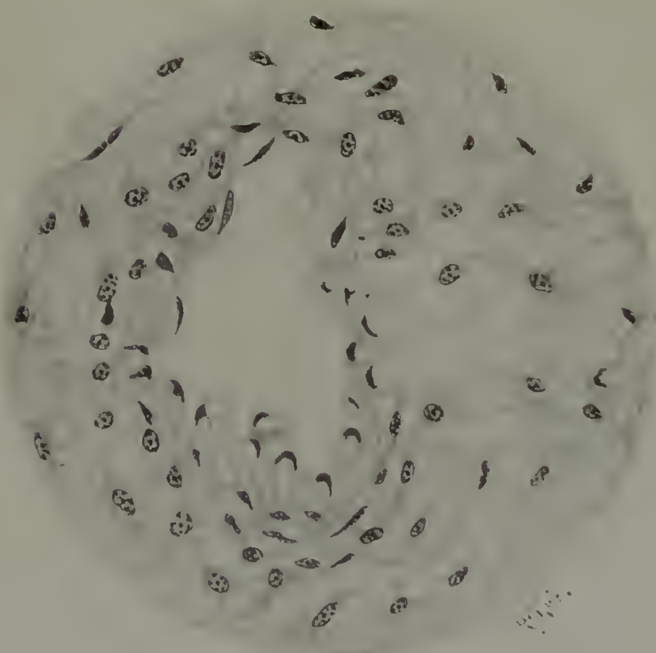


Fig. 16.—Drawing of lower part of vessel in Fig. 15. Note changes in intima, which are bulged into lumen by formation of clear intracellular spaces. Similar changes in adjacent part of wall.

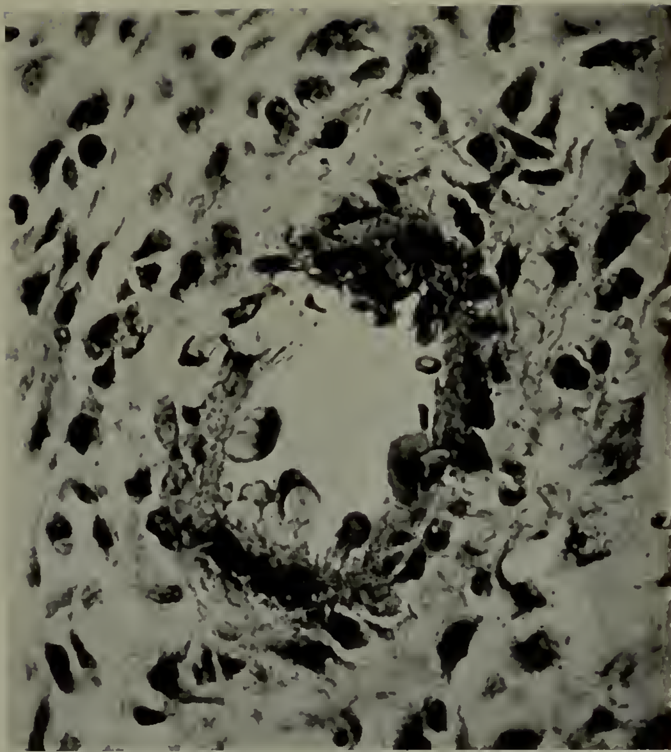


FIG. 17.—Thickened vessel in menstruating mucosa. Note remarkable changes in intimal elements. On upper left aspect wall opened out and red cell seen to be escaping. Surrounding stroma teased out.

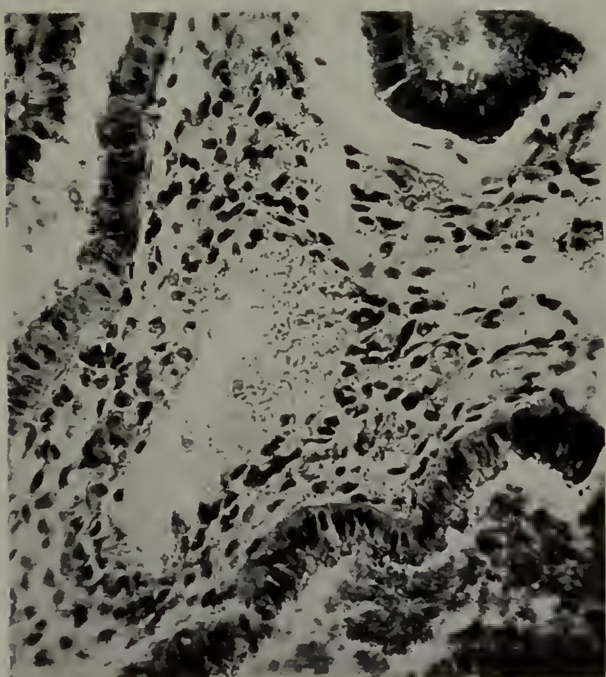


FIG. 18.—Vessel in menstrual mucosa. To right upper side wall completely opened out by wholesale displacement of intima and stroma. On this aspect there is copious hæmorrhage.

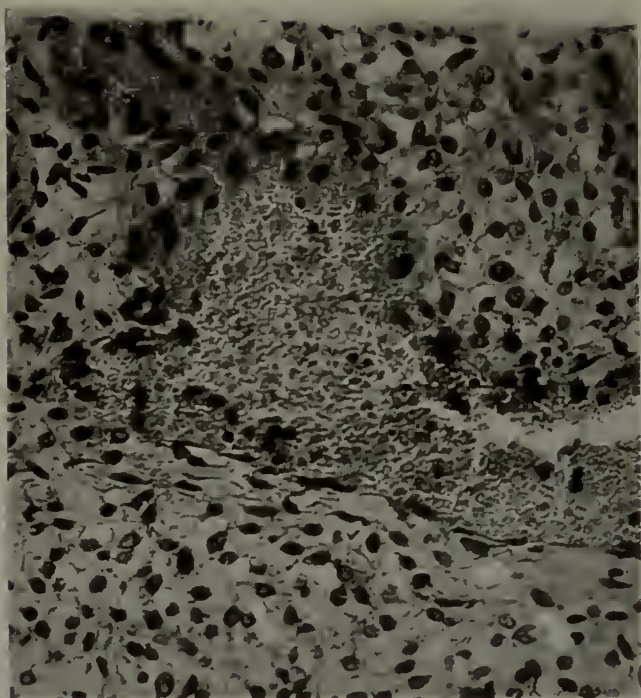


Fig. 19. Vessel in premenstrual mucosa. On lower side possesses flat intima, on upper side intima and stroma displaced, with resulting expansion of this part of wall.

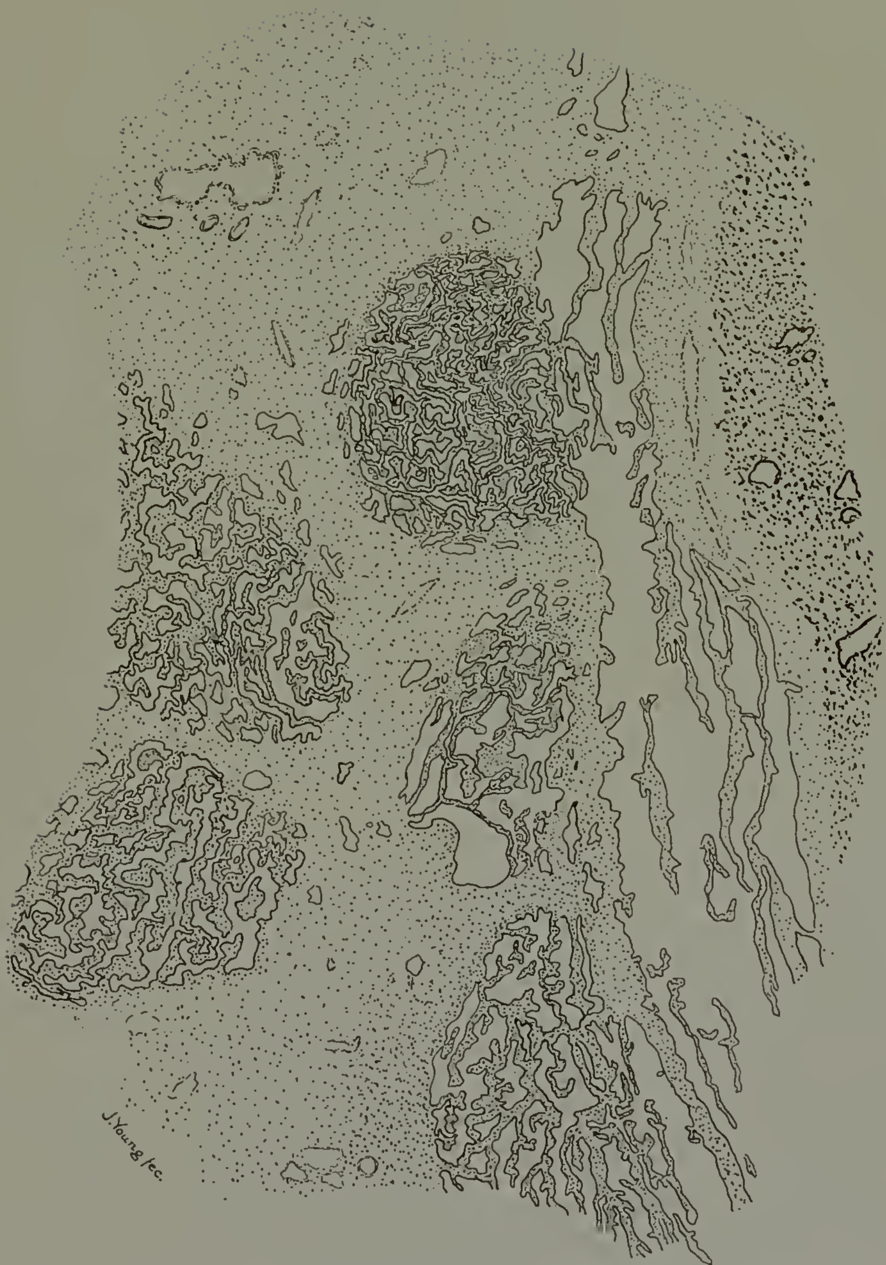


FIG. 20.—Section of tube showing on the right the villi imbedded in blood clot separated from lumen by the "capsularis." On the opposite tube wall, see complicated arrangement of spaces formed by an active epithelial proliferation.

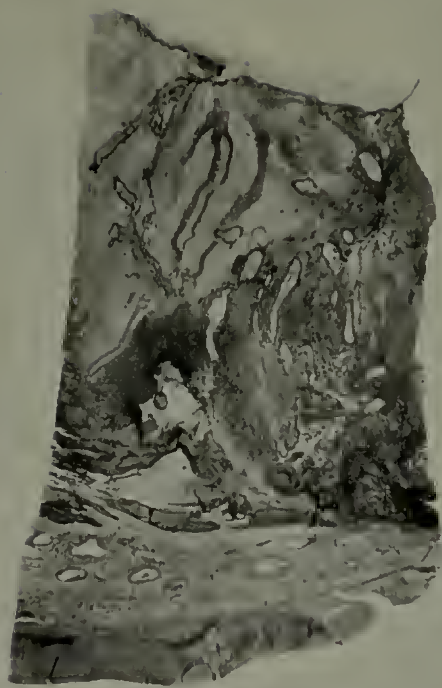


FIG. 21. — Pregnant Tube. — In upper part see amnion and chorion, from which villi project into blood-clot. In lower part tube wall shown — here a number of mucous diverticula are pesent.

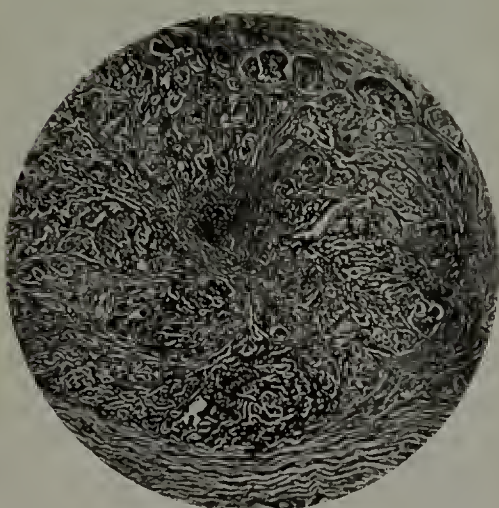


FIG. 22.—Pregnant Tube.—Section of tube on inner side of pregnancy, showing tube lumen transformed into sponge-work due to fusion of tubal folds. Section resembles fine sieve or small-meshed network.

Fig. 23.—Pregnant Tube.—To left large blood-distended diverticulum. To right see ordinary tube lumen.

Fig. 24.—Showing fine channel of communication between diverticulum and tube lumen.

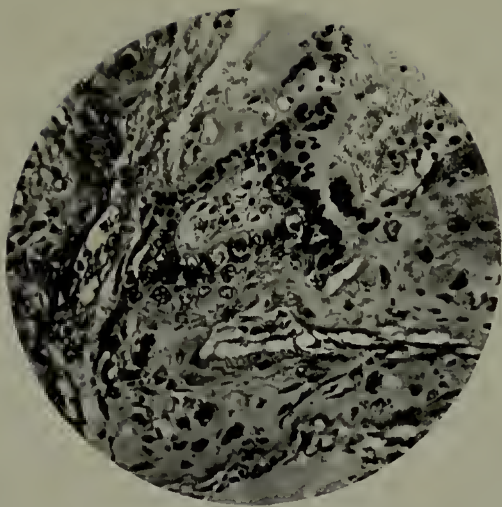


FIG. 25.—Pregnant Tube.—Tip of villus incorporated with wall of tube, which is undergoing degeneration. Note two types of chorionic epithelium — the Langhans' cells and the syncytium.

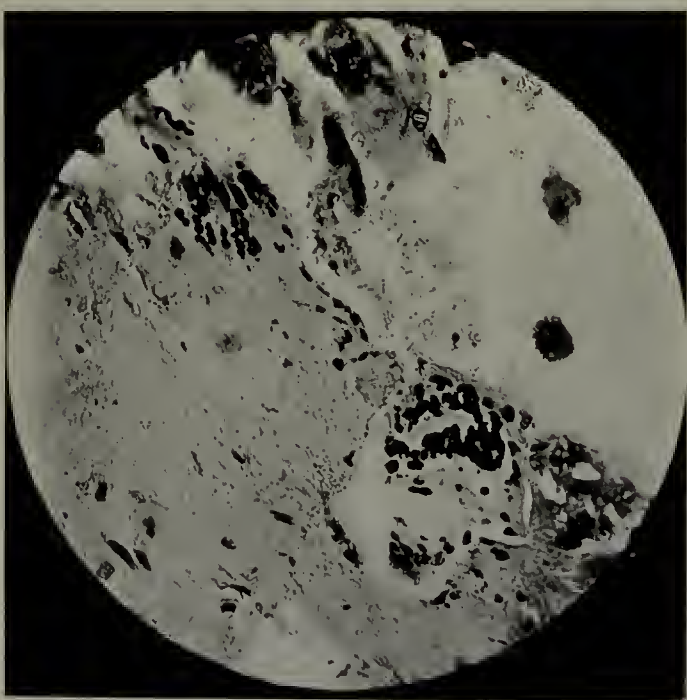


FIG. 26.—Pregnant Tube.—Mass of syncytium lying in bay formed in wall of degenerating tube.

Fig. 27.—Pregnant Tube.—Expanded vessel opening into intervillous space. In upper part see tip of villus boring its way into lumen. Below see gap in vessel wall into which villus projects. Note that the opening is larger than the entering villus. To left side see loosening of vessel wall.

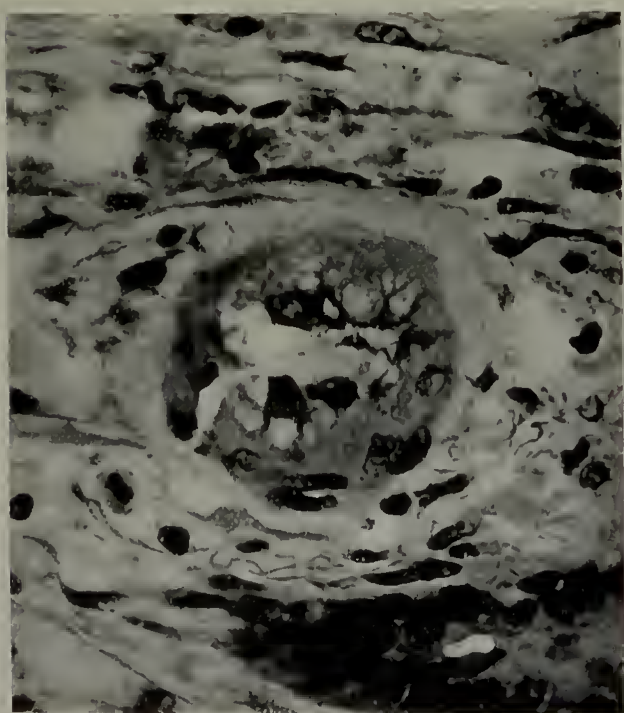


Fig. 28.—Pregnant Tube.—Small artery at distance from fœtal elements. Wall transformed into fibrinous material. Note clear spaces and tracks in vessel wall, especially towards inner aspect. Surrounding tube œdematous and degenerating.

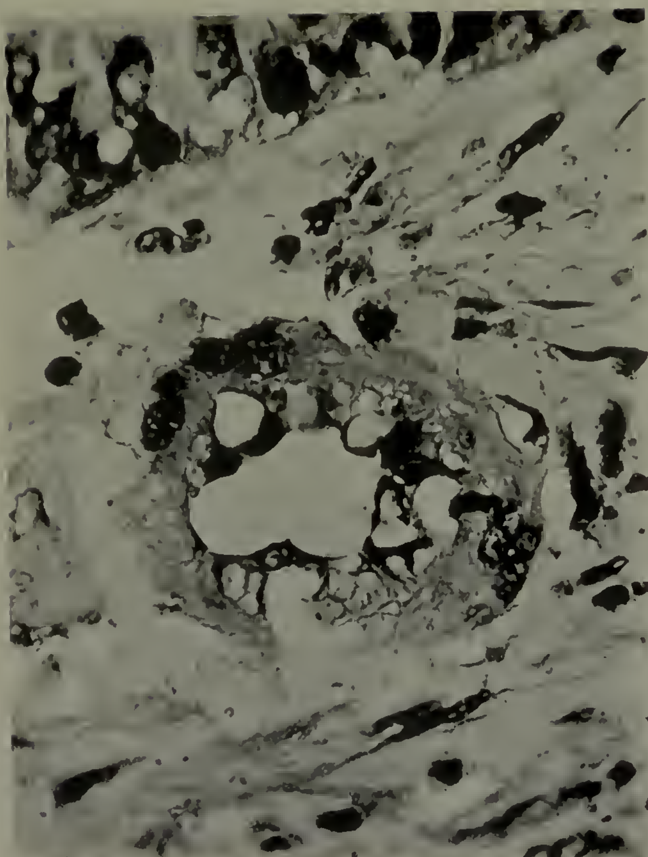


Fig. 29.—Pregnant Tube.—Small artery at long distance from chorionic elements. Wall degenerating and beset with large number of clear spaces of varying sizes, especially towards intima. In places intima swollen towards lumen. Below see track leading from intima outwards into œdematous tissues.

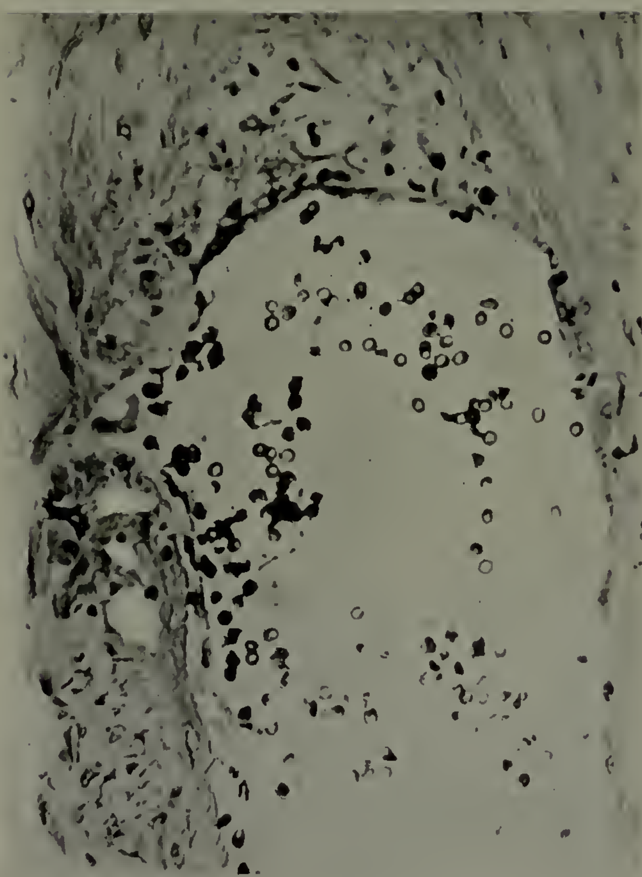


FIG. 30.—Pregnant Tube.—Vessel at long distance from chorionic elements showing marked œdematous teasing out of walls. To left side red cells leaking through track thus produced.

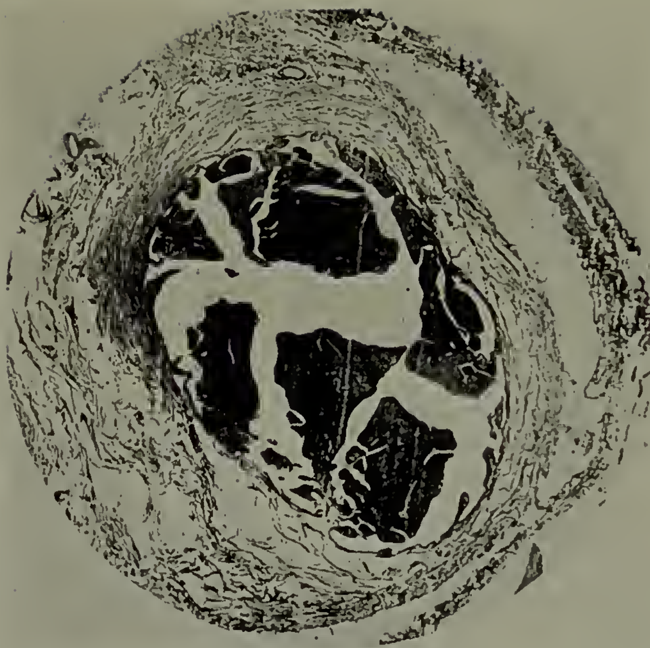


FIG. 31.—Section near uterine end of pregnant tube showing folds turgid with decidual cells. Hæmorrhage to the right; œdema and loosening of tube wall. No œdema or hæmorrhage in mucous folds.

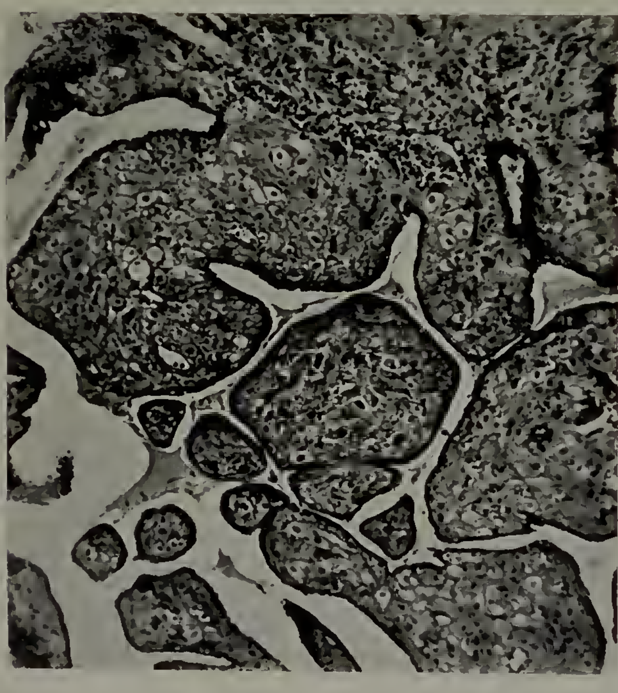


FIG. 32.—Pregnant Tube.—Higher magnification of mucous folds shown in last specimen, showing marked decidual formation. Cells enlarged and packed together as in decidua compacta of uterus.

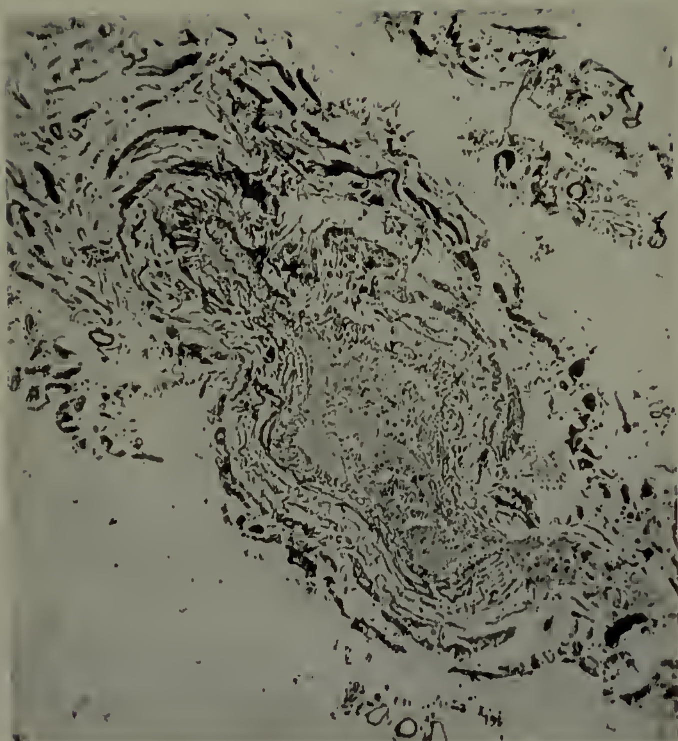


FIG. 33.—Pregnant Tube.—Thick vessel in wall of tube on inner side at long distance from pregnancy, and at same level as the sections shown in Figs. 31 and 32. No decidual formation. Vessel walls and surrounding tube ploughed up by œdema and hæmorrhage.

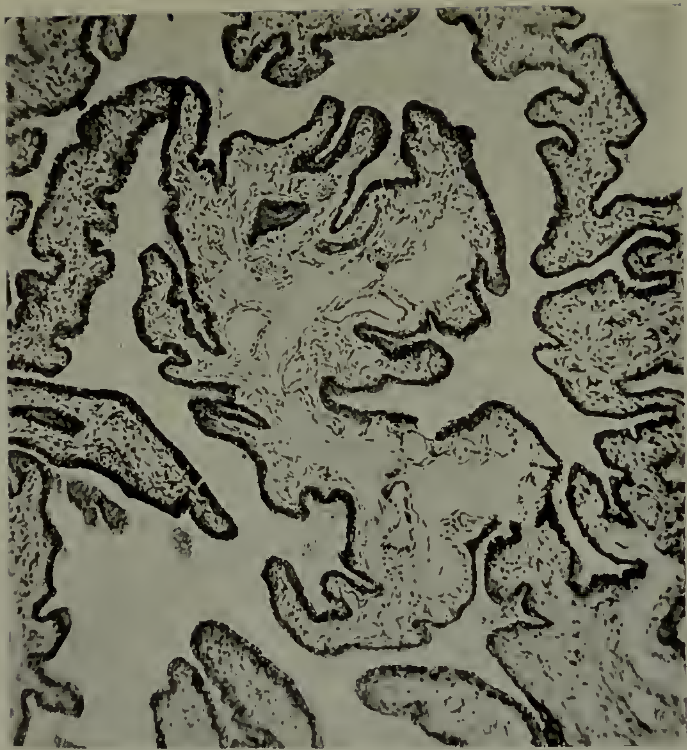


Fig. 34. Pregnant Tube.—Mucous folds with absence of decidual change. Note œdema and sinus formation.

Fig. 35.—Pregnant Tube.—Vessel containing chorionic villi. Note loosening of vessel-walls by wholesale detachment of the muscle due to œdema. To left vessel completely isolated from surrounding tube wall by great œdematous track.

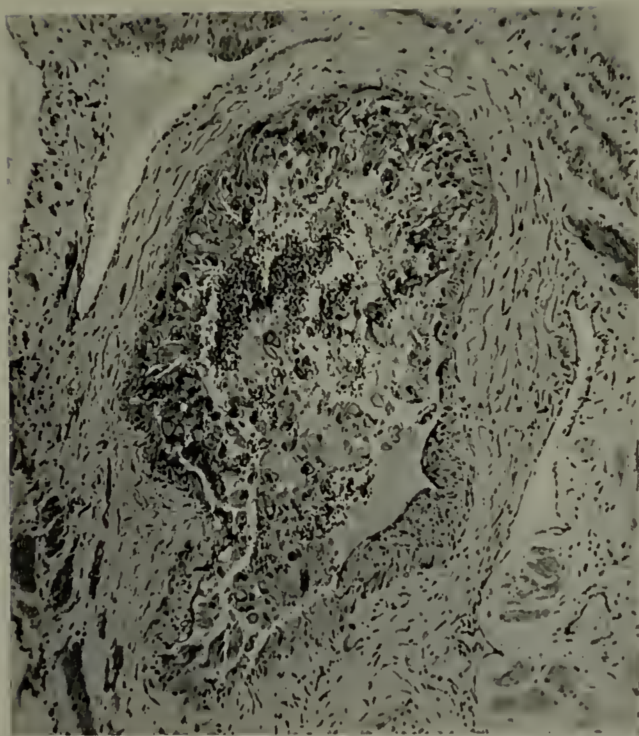


Fig. 36.—Pregnant Tube.—Vessel showing marked proliferation of endothelium, which has enlarged in a true decidual fashion. Surrounding this vessel see number of fine-walled sinuses.

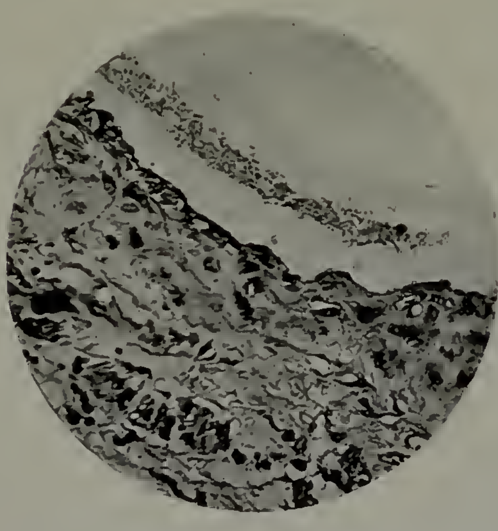


Fig. 37.—Pregnant Tube.—Vessel at distance from chorion, showing decidual enlargement of sub-endothelial elements.

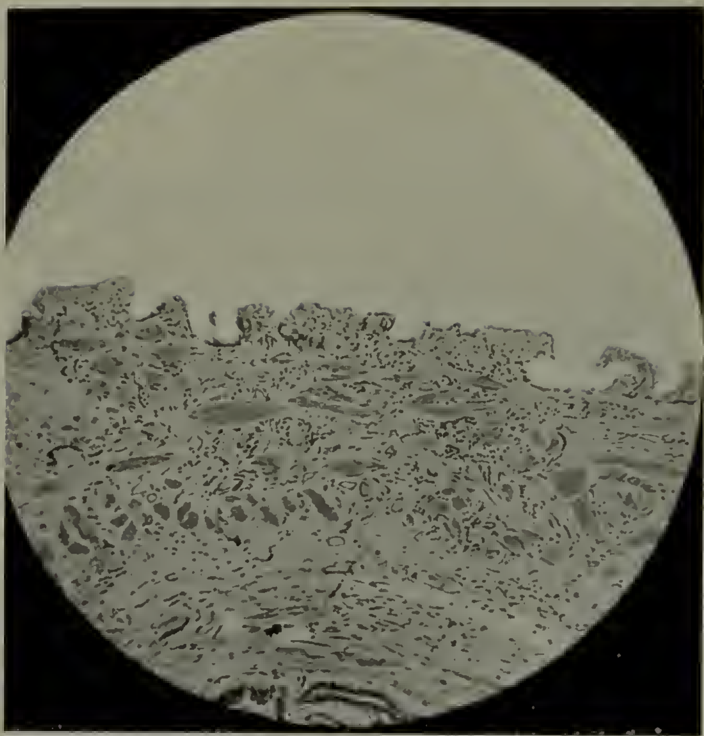


Fig. 38.—Pregnant Tube.—Peritoneal surface of tube. Note folding of surface and increase in the endothelium.

Fig. 39.—Pregnant Tube.—Higher magnification of part of peritoneal surface shown in Fig. 38. See proliferation and decidua-like enlargement of the peritoneal endothelium.

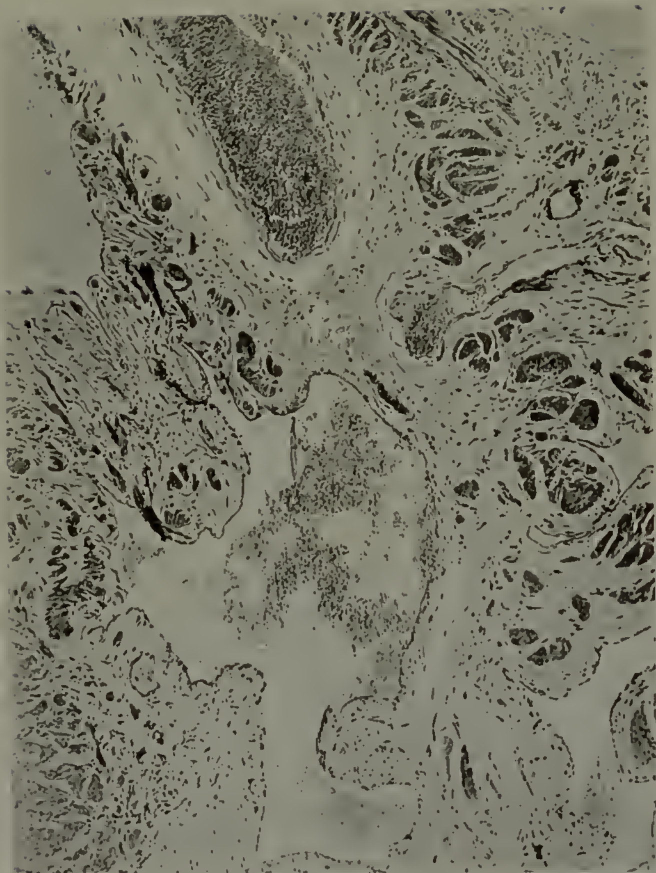


FIG. 40.—Pregnant Tube.—Blood sinuses in tubal wall. Their wall is formed by single layer of lining cells. Note the great irregularity in their contour, and the tendency to increase by the projection of offshoots into the surrounding tissues. These coincide with nothing in the ordinary tube, and must be considered as a vascular change *sui generis*.

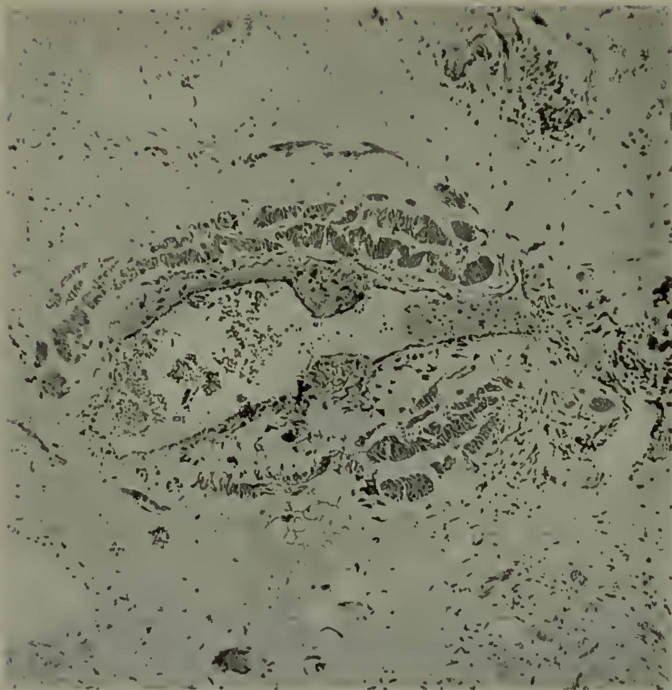


FIG. 41.—Pregnant Tube.—Blood-vessel showing almost complete isolation from surrounding tissues by œdematous escape. Note stripping-off of the supporting coats and the projection of the lumen into the surrounding tissues after the release of the intima.

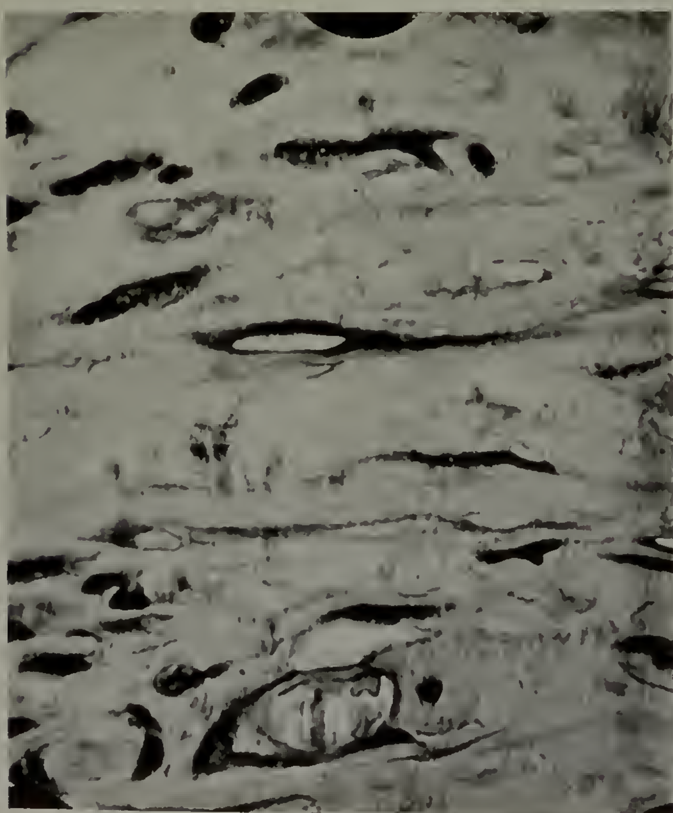


FIG. 42.—Pregnant Tube.—Degenerating portion of tube wall at distance from chorionic elements. Note "vacuolation" of connective-tissue cells. Below see mode of expansion of vessels.

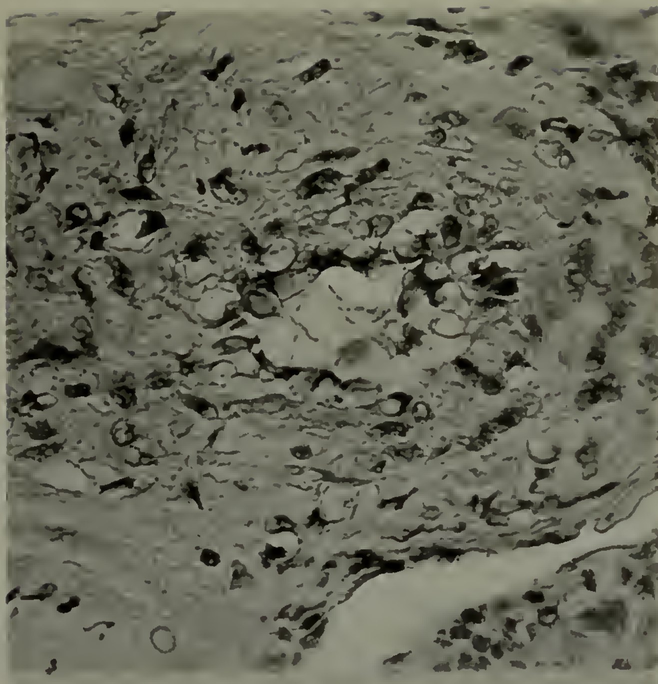


Fig. 43.—Retained Placental Fragments.—Vessel in uterine wall at distance from chorionic villi, showing fluid imbibition by endothelial and connective-tissue cells. Tissues degenerating.

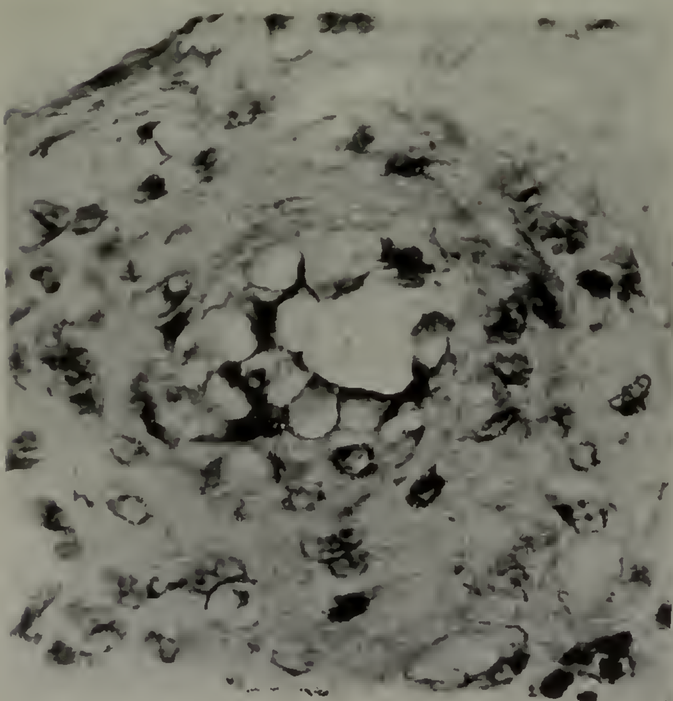


Fig. 44.—Retained Placental Fragments.—Vessel in uterine wall at distance from villi, showing foam-like appearance on inner aspect of wall due to fluid imbibition by tissue elements.

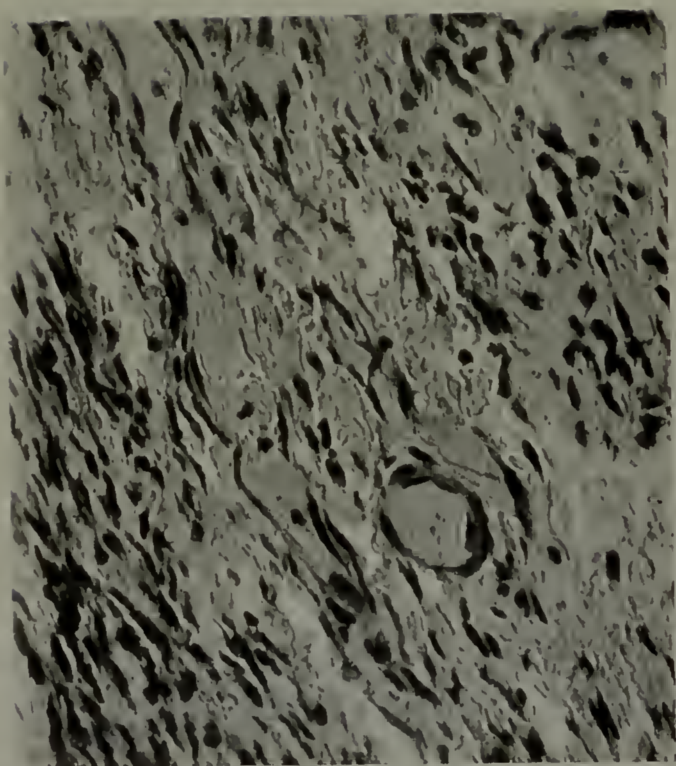


FIG. 45.—Retained Placental Fragments.—Uterine mucosa at distance from chorionic villi, showing vessel and stroma changes. Note opening out of stroma by hæmorrhage associated with stripping-off of supporting elements of vessel walls. Here and there intima also detached and blood leaking.

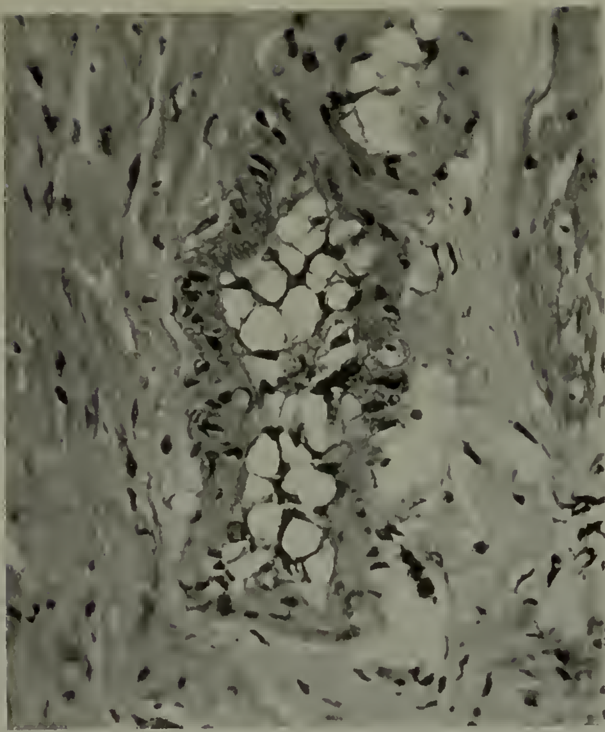


Fig. 46. – Chorionepithelioma. – Vessel in muscular wall at long distance from chorionic cells. Note froth-like appearance due to fluid imbibition by intimal and other elements of vessel wall. In lower part wall nearly completely teased out. Surrounding tissues œdematous.

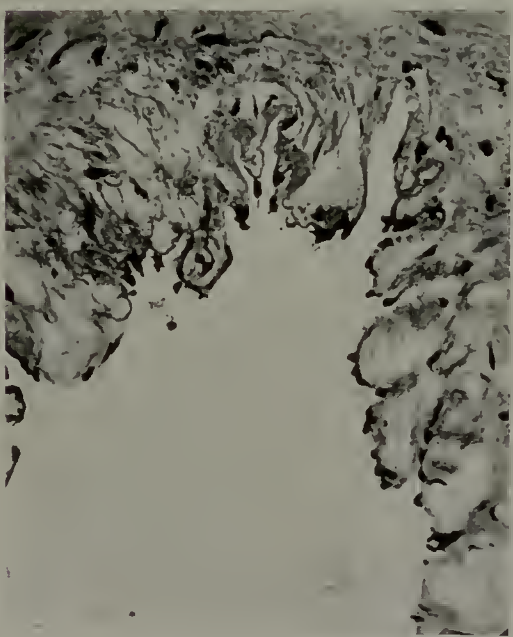


Fig. 47. —Chorionepithelioma. —Vessel in muscular wall of uterus at distance from chorionic cells. Note œdematous opening out of wall from intima outwards. In places inner aspect bulged towards lumen.

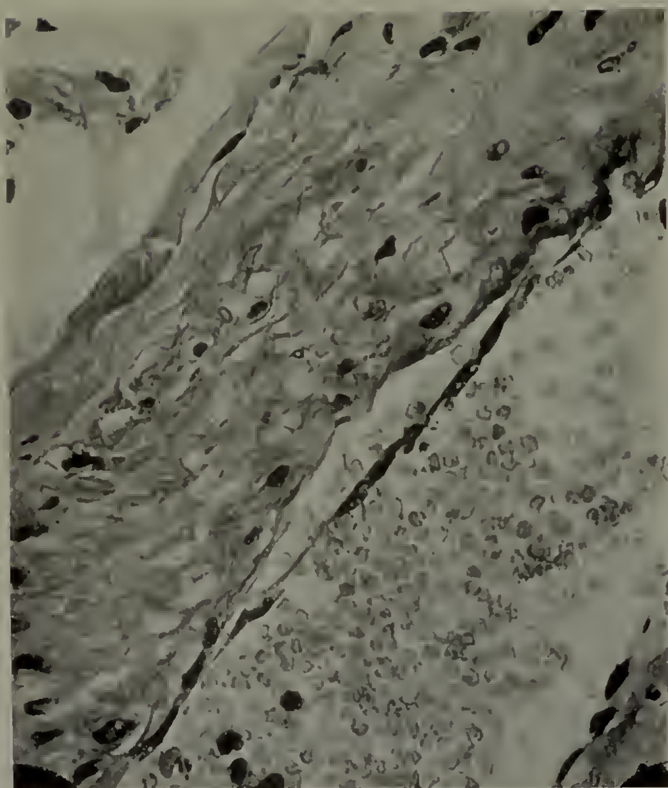


FIG. 48.—Chorionepithelioma.—Vessel in muscular wall of uterus at distance from chorionic cells. Note lifting up of endothelial sheet, under which several red cells are present, also the œdematous honeycombing of the vessel wall.

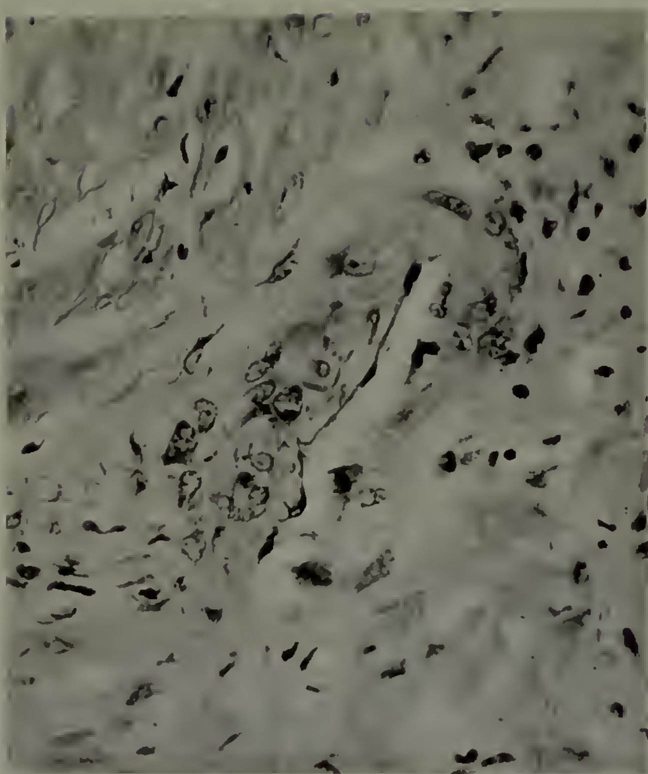


FIG. 49.—Chorionepithelioma.—Vessel in uterine wall at little distance from chorionic cells. On left side see swelling of cells in a decidua-like fashion. On right side (towards which the chorionic cells are advancing) the wall is markedly degenerated and almost completely opened out by a displacement and solution. Surrounding tissues degenerating and œdematous.

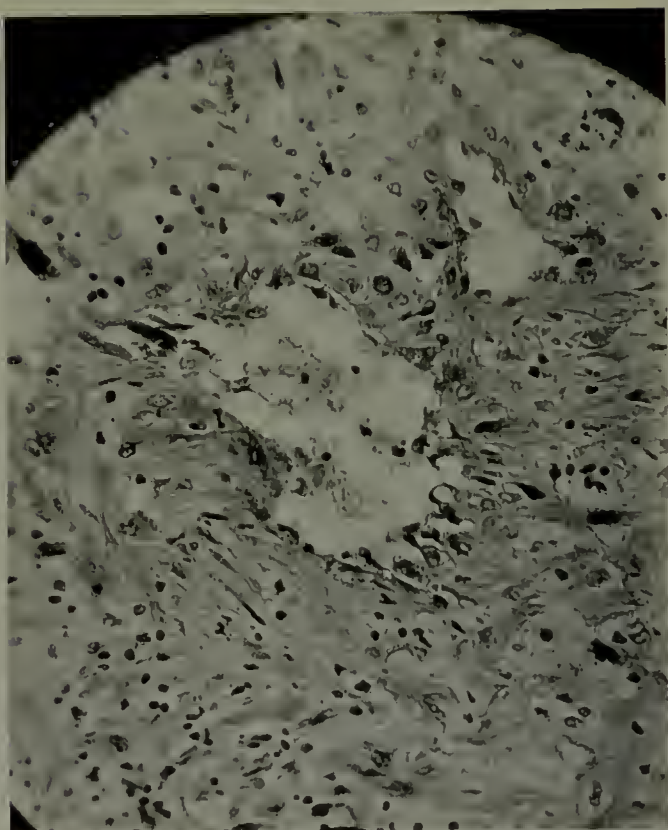


FIG. 50.—Chorionepithelioma.—Uterine wall at distance from chorionic cells, showing fine vessel in process of expansion. Note irregular and, in places, ragged contour. Below see distinct evidence of fluid imbibition by cells, which precedes the opening out of the wall. Surrounding tissues œdematous.

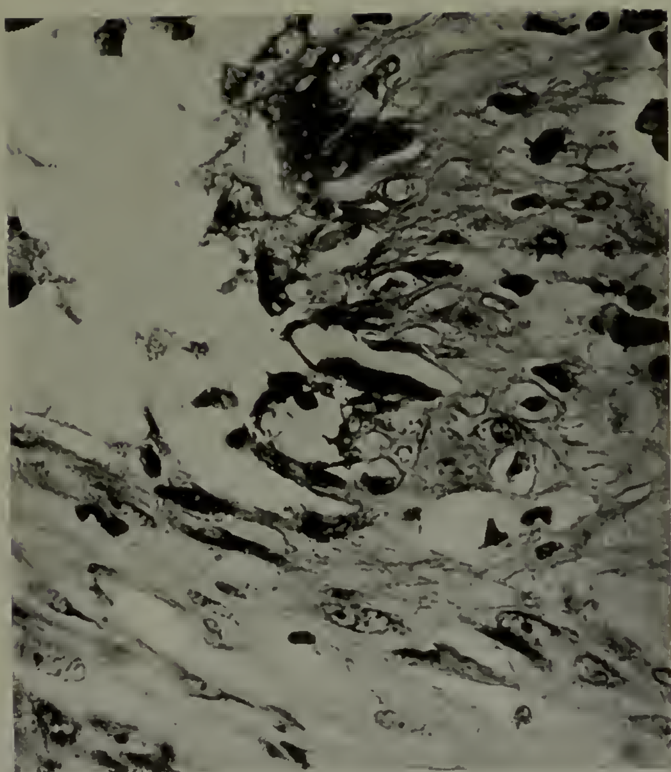


FIG. 51.—Chorionepithelioma.—Vessel in uterine wall showing ragged wall in process of expansion. Note fluid accumulation towards lining surface. In one place the fine cell film has given way, with a corresponding increase in the lumen in that part. Above this see elongated fluid track in cell. These appearances suggest the mode in which capillary budding occurs (*cf.* Plates VII. and VIII.).

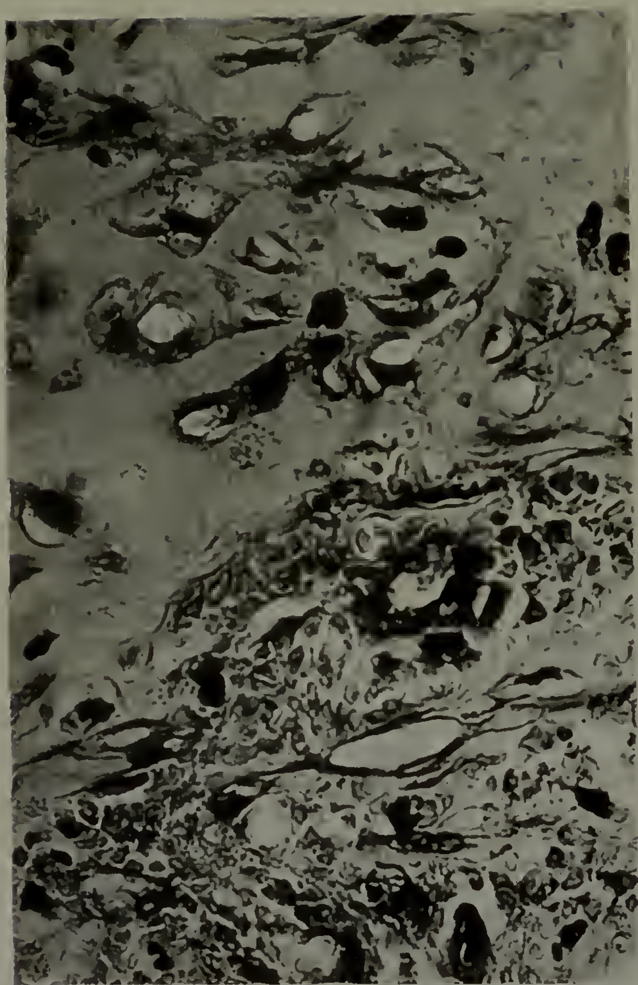


FIG. 52.—Chorionepithelioma.—Connective-tissue cells in uterine wall at distance from chorionic elements, showing intracellular fluid accumulation. Hæmorrhage below. Tissues degenerating.

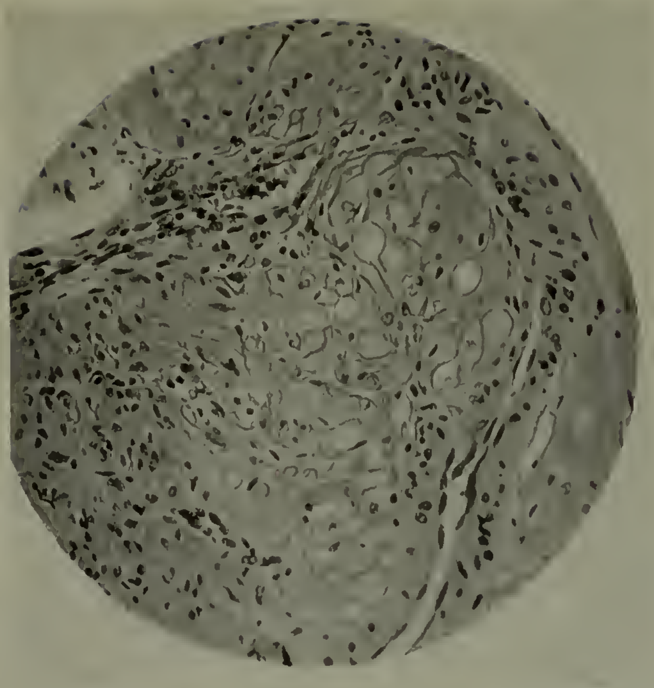


Fig. 53.—Chorionepithelioma.—Intermuscular connective-tissue cells enlarged, many in a decidua-like fashion.

Fig. 54.—Chorionepithelioma.—Mass of chorionic epithelium in aneurismal expansion of a fine-walled vessel. Note the distinct endothelial layer. There is an œdematous separation of the tissues, but little evidence of disintegration at this level.

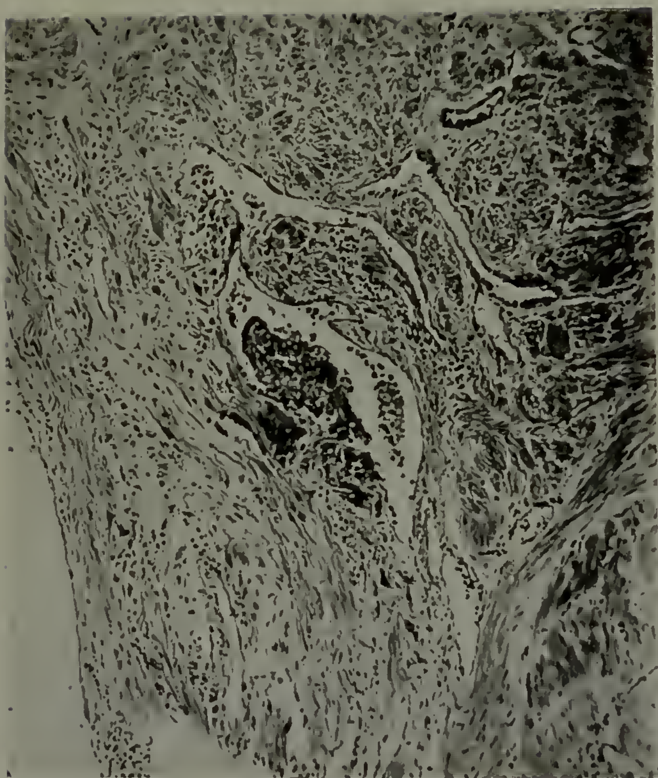


FIG. 55. Chorionepithelioma. Portion of muscular wall of uterus. To left and below see part of greatly expanded blood-sinus. In centre see expanded fine-walled vessel in lumen, and attached to one wall of which, see chorionic clump. Note distinct endothelial layer and fact that the vessel narrows to meagre size above. Round about see expanded vessels.

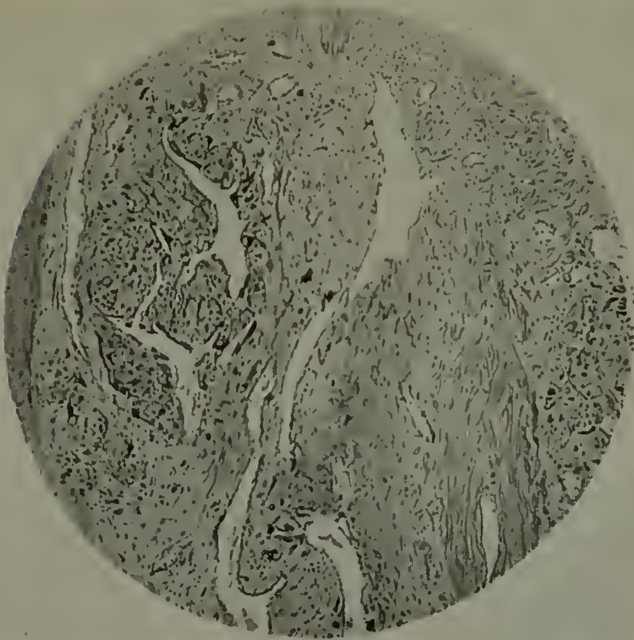


FIG. 56.—Chorionepithelioma.—Portion of muscular wall of uterus. To left see mass of chorionic cells. Surrounding this have large number of expanded, fine-walled vessels, some of which exhibit irregular contour.

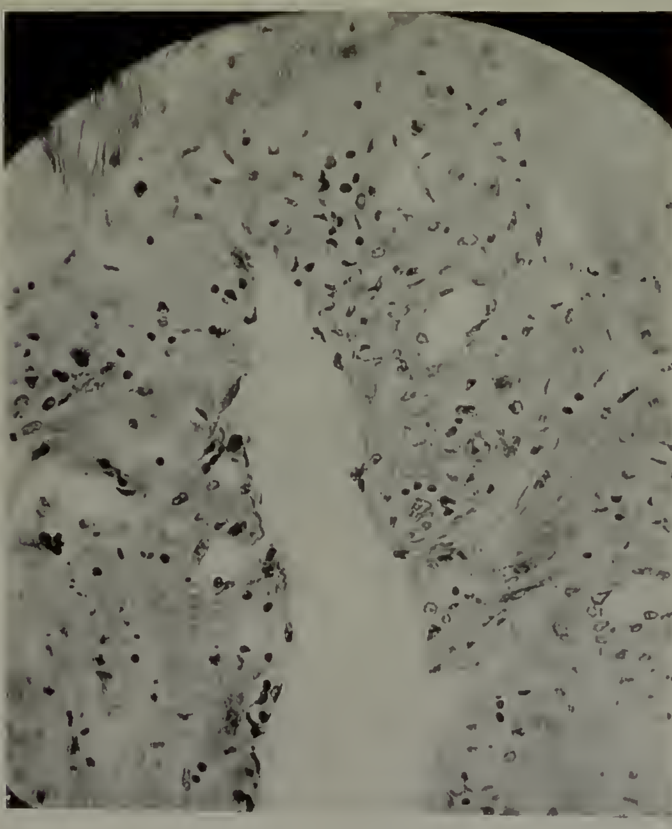


FIG. 57.—Chorionepithelioma.—Portion of expanded vessel to right of chorionic mass in Fig. 56, under higher magnification. In places intima present; in other places wholesale crumbling away and opening out of the wall by displacement and solution. This is one way in which the blood tracks actually advance towards the chorionic cells. In this case there is a marked solution of tissue, as contrasted with the vessels in Figs. 54 and 55, where it is absent.

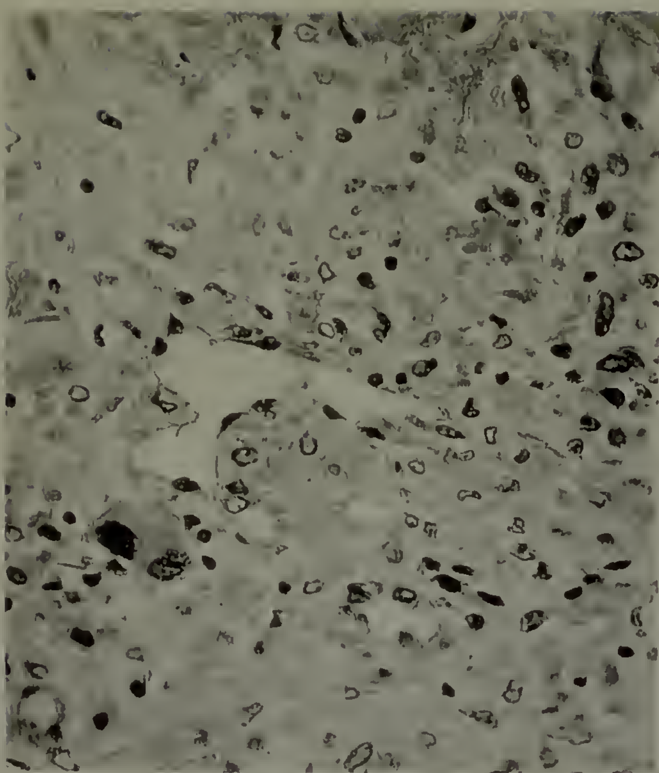


Fig. 58.—Chorionepithelioma.—Mass of fœtal syncytium near vessel. The surrounding connective-tissue cells are enlarged in a decidua-like manner.

FIG. 59.—Teacher-Bryce Earliest Human Ovum.—1 and 7 necrotic lamina of decidua; 2 and 6 spongework formed by plasmodium; 4 portal of entrance; 3 and 5 cyto-trophoblast; 8 and 12 glands; 9 vessel in decidua opening into ovum cavity; 10 and 11 ditto, with plasmodial masses projecting into their lumina. (From *Early Development and Imbedding of the Human Ovum.*—Bryce and Teacher.)

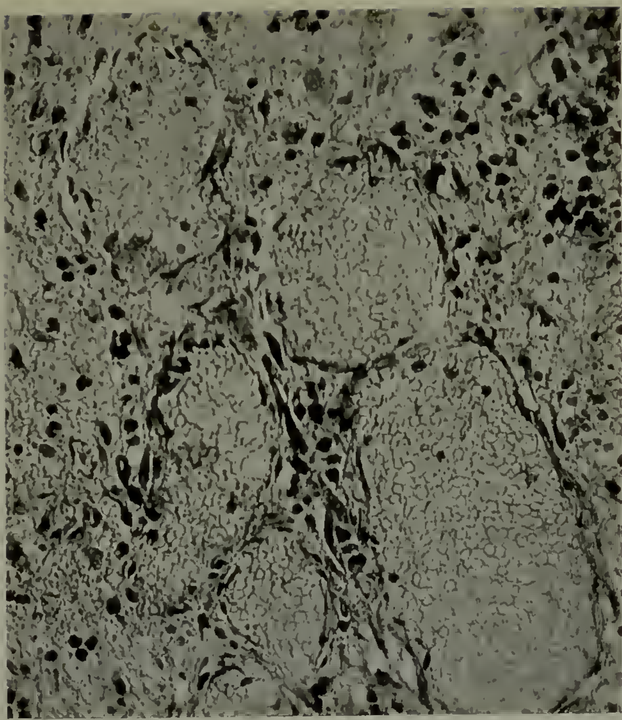


Fig. 60.—Early Human Ovum.—Expanded vessels in mucosa at small distance from blood cavity. Note teasing out of their walls by separation of the supporting elements and, in places, of the intima. Free blood leakage.

Fig. 61.—Vessel in muscular wall of pregnant uterus, showing œdematous opening out of wall. Surrounding tissues œdematous (3 months).

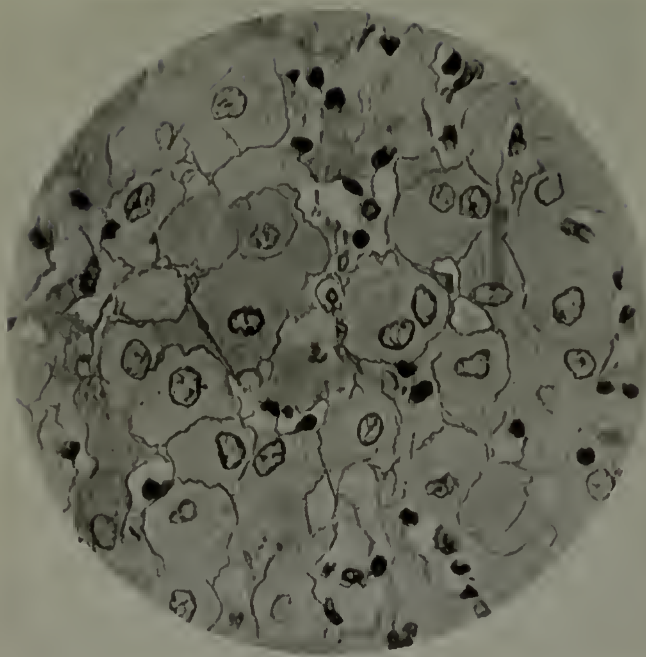


FIG. 62.—Uterine Decidua.—Greatly enlarged stroma cells, some of which are in process of dividing and contain two nuclei. In other places see appearances which suggest a recent division—two nuclei lying together separated by "cell-membrane."

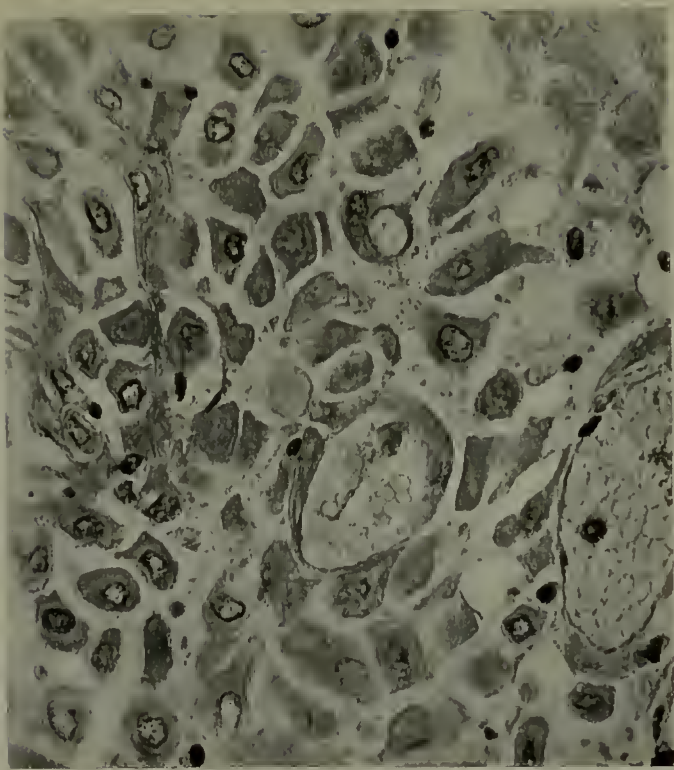


Fig. 63.—Uterine Decidua.—To show especially the small vessel near the centre of the field, the endothelial cells of which have enlarged in a decidual fashion. The surrounding decidual cells have, as often happens, shrunk considerably in the process of hardening.

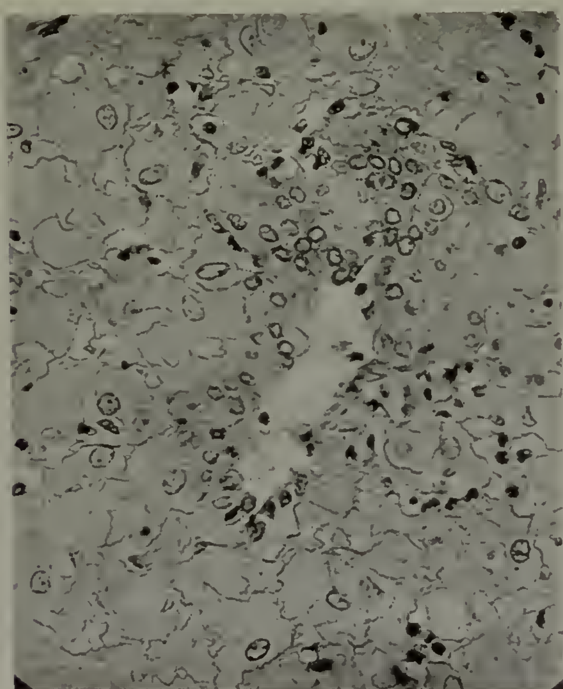


Fig. 64.—Uterine Decidua.—Section from the vera showing proliferation and enlargement of the endothelial cells of a vessel.

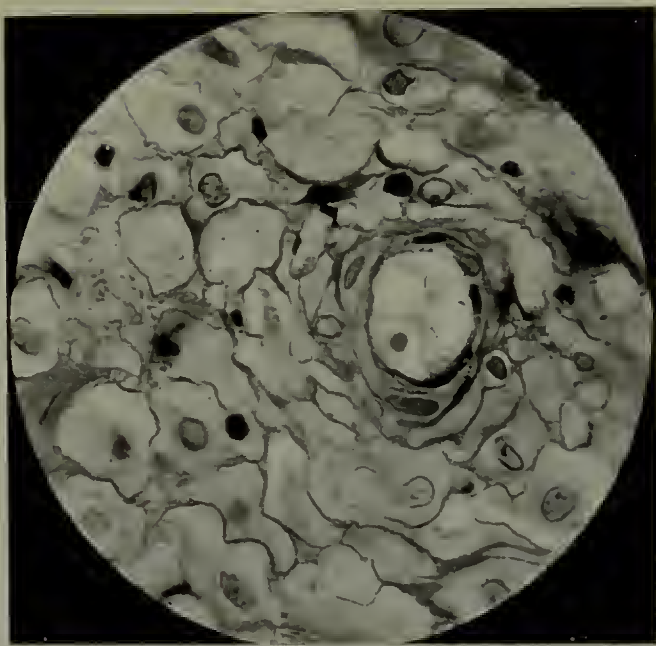


FIG. 65.—Uterine Decidua.—Showing how the decidual change involves the cells of the vessel wall. The close packing together of the supporting cells prevents the usual enlargement, which is seen to become more and more evident as the looser stroma is reached.

FIG. 66.—Vessel in muscular wall of pregnant uterus. Note proliferation of endothelium and a decidual enlargement of the cells. Here and there see endothelial vacuolation. Vessel wall and surrounding tissues œdematous.

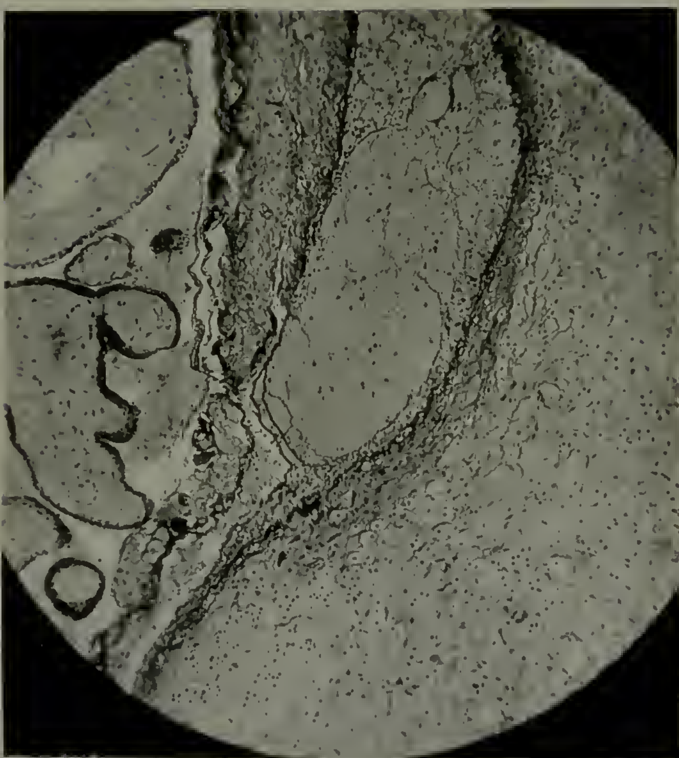


FIG. 67.—Young Ovum.—To the left see the implantation chamber with the villi. Into it a maternal vessel is opening. There is a well-marked decidual change in the surrounding stroma, and, even at this early stage (17 or 18 days), the œdema and hæmorrhage present in the youngest ova are completely absent.

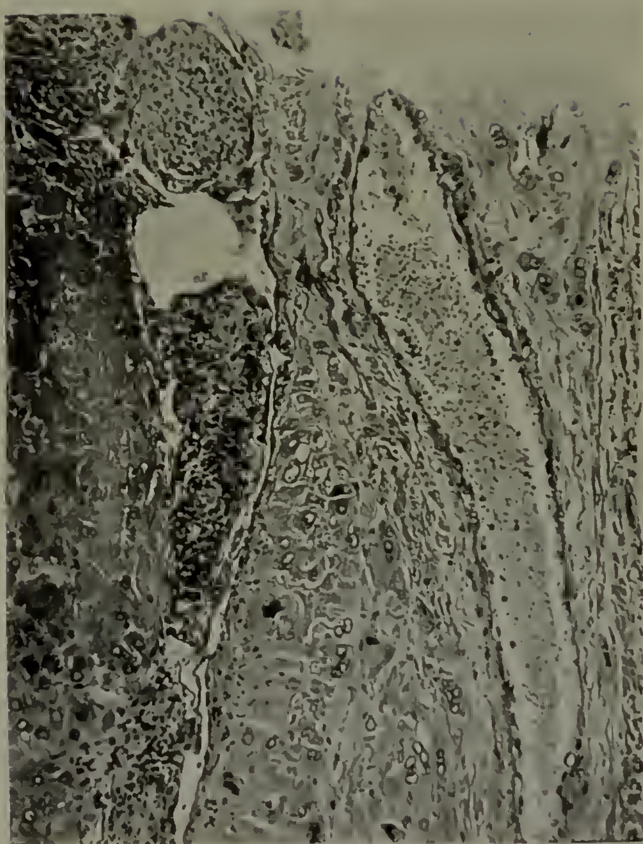


FIG. 68.—Uterine Decidua.—Section from deepest part of decidua serotina. To left see vessel containing fœtal villus. There is a well-marked decidual change in the surrounding stroma.